ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of solution for injection, equivalent to 500 IU insulin, or 10 ml of solution for injection, equivalent to 1000 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Rapid is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a vial.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required. Insulin Human Winthrop Rapid is also suitable for the treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Rapid is injected subcutaneously 15 to 20 minutes before a meal.

In the treatment of severe hyperglycaemia or ketoacidosis in particular, insulin administration is part of a complex therapeutic regimen which includes measures to protect patients from possible severe complications of a relatively rapid lowering of blood glucose. This regimen requires close monitoring (metabolic status, acid-base and electrolyte status, vital parameters etc.) in an intensive care unit or similar setting.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,

- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Insulin Human Winthrop Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in an intensive care unit or under comparable monitoring and treatment conditions (see "Daily doses and timing of administration").

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Rapid
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema;

MedDRA system organ classes	Common	Uncommon	Not known
			Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Rapid must not be mixed with insulin human formulations designed specifically for use in insulin pumps.

Insulin Human Winthrop Rapid must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storageconditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml solution in a vial and 10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of the dose.

Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Rapid may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps
Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/011
EU/1/06/368/012
EU/1/06/368/169
EU/1/06/368/170

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 40 IU/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of solution for injection, equivalent to 400 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Rapid is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a vial.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required. Insulin Human Winthrop Rapid is also suitable for the treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Rapid is injected subcutaneously 15 to 20 minutes before a meal.

In the treatment of severe hyperglycaemia or ketoacidosis in particular, insulin administration is part of a complex therapeutic regimen which includes measures to protect patients from possible severe complications of a relatively rapid lowering of blood glucose. This regimen requires close monitoring (metabolic status, acid-base and electrolyte status, vital parameters etc.) in an intensive care unit or similar setting.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,

- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Insulin Human Winthrop Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in an intensive care unit or under comparable monitoring and treatment conditions (see "Daily doses and timing of administration").

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Rapid
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Rapid must not be mixed with insulin human formulations designed specifically for use in insulin pumps.

Insulin Human Winthrop Rapid must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of the dose.

Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Rapid may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps.Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/001
EU/1/06/368/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of solution for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Rapid is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required. Insulin Human Winthrop Rapid is also suitable for the treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Rapid is injected subcutaneously 15 to 20 minutes before a meal.

In the treatment of severe hyperglycaemia or ketoacidosis in particular, insulin administration is part of a complex therapeutic regimen which includes measures to protect patients from possible severe complications of a relatively rapid lowering of blood glucose. This regimen requires close monitoring (metabolic status, acid-base and electrolyte status, vital parameters etc.) in an intensive care unit or similar setting.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,

- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

Insulin Human Winthrop Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Insulin Human Winthrop Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in an intensive care unit or under comparable monitoring and treatment conditions (see "Daily doses and timing of administration").

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Rapid
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of

carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Rapid cartridges
The Insulin Human Winthrop Rapid cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Rapid in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Rapid in 1 unit dose increments.
These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site	Injection site reactions	Injection site urticaria	Injection site inflammation;

MedDRA system organ classes	Common	Uncommon	Not known
conditions			Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling;

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Rapid must not be mixed with insulin human formulations designed specifically for use in insulin pumps.

Insulin Human Winthrop rapid must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge
The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Rapid cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the solution may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Rapid must be kept at room temperature for 1 to 2 hours.
Inspect the cartridge before use. Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Rapid may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Rapid cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/088
EU/1/06/368/013
EU/1/06/368/014
EU/1/06/368/093
EU/1/06/368/098
EU/1/06/368/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid SoloStar 100 IU/ml solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of solution for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Rapid is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Rapid is injected subcutaneously 15 to 20 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Rapid

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Rapid must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Empty pens must never be re-used and must be properly discarded.

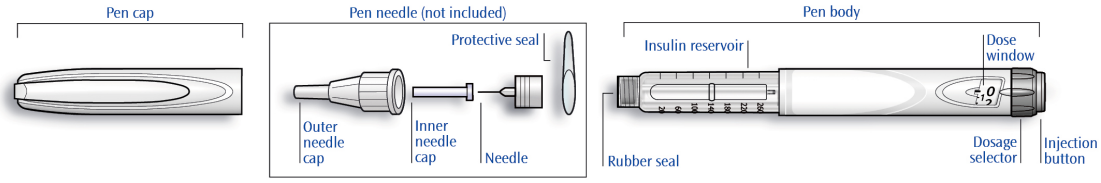
To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin solution (Insulin Human Winthrop Rapid) must be clear, colourless, with no solid particles visible, and must have a water-like consistency. Do not use this SoloStar if insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly.
If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/113
EU/1/06/368/114
EU/1/06/368/115
EU/1/06/368/116

EU/1/06/368/117
EU/1/06/368/118

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin, or 10 ml of suspension for injection, equivalent to 1000 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Basal is an isophane insulin suspension.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Basal is injected subcutaneously 45 to 60 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Basal is administered subcutaneously. Insulin Human Winthrop Basal must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Basal for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Basal, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Basal
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Basal can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting, ATC Code: A10AC01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Basal (an isophane insulin suspension) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 60 minutes, the phase of maximum action is between 3 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Basal must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Basal must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Basal must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml suspension in a vial and 10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Basal may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/020
EU/1/06/368/021
EU/1/06/368/171
EU/1/06/368/172

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 40 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Basal is an isophane insulin suspension.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Basal is injected subcutaneously 45 to 60 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Basal is administered subcutaneously. Insulin Human Winthrop Basal must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Fur further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Basal for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Basal, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Basal
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Basal can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting, ATC Code: A10AC01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Basal (an isophane insulin suspension) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 60 minutes, the phase of maximum action is between 3 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Basal must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Basal must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Basal must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storageconditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Basal may be mixed with all insulin human formulation, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/003
EU/1/06/368/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Basal is an isophane insulin suspension.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a cartridge.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Basal is injected subcutaneously 45 to 60 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insulin Human Winthrop Basal is administered subcutaneously. Insulin Human Winthrop Basal must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Basal for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Basal, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Basal
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Basal cartridges
The Insulin Human Winthrop Basal cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Basal in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Basal in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Basal can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting, ATC Code: A10AC01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Basal (an isophane insulin suspension) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 60 minutes, the phase of maximum action is between 3 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Basal must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Basal must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Basal must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge
The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.

The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Basal cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the suspension may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Basal must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Basal may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Basal cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/089
EU/1/06/368/022
EU/1/06/368/023
EU/1/06/368/094
EU/1/06/368/099
EU/1/06/368/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Basal is an isophane insulin suspension.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Basal is injected subcutaneously 45 to 60 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Basal is administered subcutaneously. Insulin Human Winthrop Basal must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Basal for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Basal, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Basal

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Basal can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting, ATC Code: A10AC01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Basal (an isophane insulin suspension) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 60 minutes, the phase of maximum action is between 3 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Basal must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Basal must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, Insulin Human Winthrop Basal must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

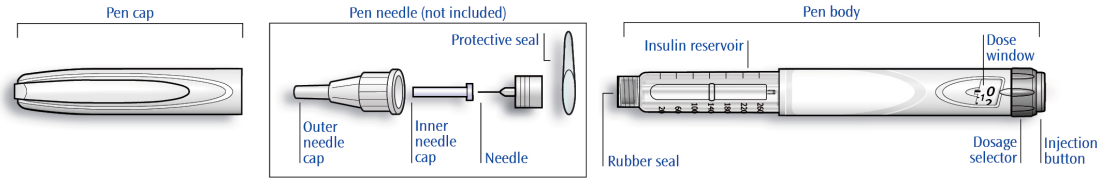
To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin suspensions (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures) should be mixed by turning SoloStar up and down at least 10 times to resuspend the insulin. The pen should be turned gently to avoid foaming in the cartridge. After mixing, the insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/119
EU/1/06/368/120
EU/1/06/368/121

EU/1/06/368/122
EU/1/06/368/123
EU/1/06/368/124

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 15 is a biphasic isophane insulin suspension consisting of 15% dissolved insulin and 85% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 15 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 15 is administered subcutaneously. Insulin Human Winthrop Comb 15 must never be injected intravenously.

Insulin absorption and hence the blood–glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 15 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 15, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 15
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 15 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 15 (a biphasic isophane insulin suspension with 15% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 15 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 15 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 15 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C -8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 15 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/029
EU/1/06/368/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 40 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 15 is a biphasic isophane insulin suspension consisting of 15% dissolved insulin and 85% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 15 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 15 is administered subcutaneously. Insulin Human Winthrop Comb 15 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 15 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 15, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 15
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 15 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 15 (a biphasic isophane insulin suspension with 15% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data
The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 15 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 15 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 15 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 15 may be mixed with all insulin human fomulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/005
EU/1/06/368/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 15 is a biphasic isophane insulin suspension consisting of 15% dissolved insulin and 85% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injectionin a cartridge.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 15 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insulin Human Winthrop Comb 15 is administered subcutaneously. Insulin Human Winthrop Comb 15 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 15 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 15, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 15
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Comb 15 cartridges
The Insulin Human Winthrop Comb 15 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Comb 15 in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Comb 15 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 15 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

*Metabolism and nutrition disorders*Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,

- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 15 (a biphasic isophane insulin suspension with 15% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 15 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 15 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 15 must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge

The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Comb 15 cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the suspension may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Comb 15 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new

cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 15 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Comb 15 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/090
EU/1/06/368/031
EU/1/06/368/032
EU/1/06/368/095
EU/1/06/368/100
EU/1/06/368/033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 15 is a biphasic isophane insulin suspension consisting of 15% dissolved insulin and 85% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 15 is injected subcutaneously 30 to 45 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Comb 15 is administered subcutaneously. Insulin Human Winthrop Comb 15 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 15 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 15, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 15

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 15 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 15 (a biphasic isophane insulin suspension with 15% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 15 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 15 must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, Insulin Human Winthrop Comb 15 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

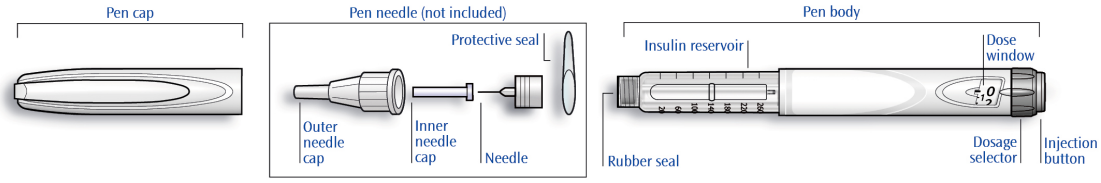
It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen

The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin suspensions (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures) should be mixed by turning SoloStar up and down at least 10 times to resuspend the insulin. The pen should be turned gently to avoid foaming in the cartridge. After mixing, the insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/125
EU/1/06/368/126
EU/1/06/368/127

EU/1/06/368/128
EU/1/06/368/129
EU/1/06/368/130

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 25 is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 25 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if

- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 25 is administered subcutaneously. Insulin Human Winthrop Comb 25 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 25 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 25, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 25

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of

carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 25 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 25 (a biphasic isophane insulin suspension with 25% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 25 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 25 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 25 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 25 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/038
EU/1/06/368/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 40 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 25 is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 25 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 25 is administered subcutaneously. Insulin Human Winthrop Comb 25 must never be injected intravenously.

Insulin absorption and hence the blood–glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 25 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 25, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 25
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 25 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 25 (a biphasic isophane insulin suspension with 25% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 25 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 25 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 25 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 25 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/007
EU/1/06/368/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 25 is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a cartridge.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 25 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insulin Human Winthrop Comb 25 is administered subcutaneously. Insulin Human Winthrop Comb 25 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 25 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 25, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 25
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Comb 25 cartridges
The Insulin Human Winthrop Comb 25 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Comb 25 in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Comb 25 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 25 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,

- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 25 (a biphasic isophane insulin suspension with 25% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 25 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 25 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 25 must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge
The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Comb 25 cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the suspension may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Comb 25 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new

cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 25 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Comb 25 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/091
EU/1/06/368/040
EU/1/06/368/041
EU/1/06/368/096
EU/1/06/368/101
EU/1/06/368/042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 25 is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 25 is injected subcutaneously 30 to 45 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Comb 25 is administered subcutaneously. Insulin Human Winthrop Comb 25 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 25 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 25, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 25

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 25 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 25 (a biphasic isophane insulin suspension with 25% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 25 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 25 must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, Insulin Human Winthrop Comb 25 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

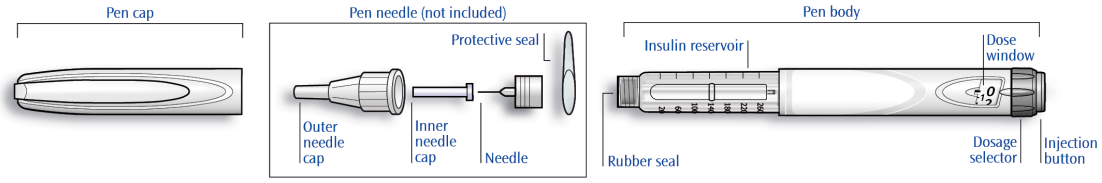
To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin suspensions (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures) should be mixed by turning SoloStar up and down at least 10 times to resuspend the insulin. The pen should be turned gently to avoid foaming in the cartridge. After mixing, the insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/131
EU/1/06/368/132
EU/1/06/368/133

EU/1/06/368/134
EU/1/06/368/135
EU/1/06/368/136

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin, or 10 ml of suspension for injection, equivalent to 1000 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 30 is a biphasic isophane insulin suspension consisting of 30% dissolved insulin and 70% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 30 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 30 is administered subcutaneously. Insulin Human Winthrop Comb 30 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 30 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 30, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 30
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,

- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors

Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 30 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain ; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 30 (a biphasic isophane insulin suspension with 30% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 30 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 30 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 30 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 30 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml suspension in a vial and 10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 30 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/143
EU/1/06/368/144
EU/1/06/368/173
EU/1/06/368/174

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 30 is a biphasic isophane insulin suspension consisting of 30% dissolved insulin and 70% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a cartridge.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 30 is injected subcutaneously 30 to 45 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insulin Human Winthrop Comb 30 is administered subcutaneously. Insulin Human Winthrop Comb 30 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 30 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 30, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 30
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Comb 30 cartridges
The Insulin Human Winthrop Comb 30 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Comb 30 in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Comb 30 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 30 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,

- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 30 (a biphasic isophane insulin suspension with 30% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 30 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 30 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 30 must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge

The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 30 next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Comb 30 cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the suspension may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Comb 30 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new

cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 30 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concernig incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Comb 30 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinalproduct or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/145
EU/1/06/368/146
EU/1/06/368/147
EU/1/06/368/148
EU/1/06/368/149
EU/1/06/368/150

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 30 is a biphasic isophane insulin suspension consisting of 30% dissolved insulin and 70% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 30 is injected subcutaneously 30 to 45 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Comb 30 is administered subcutaneously. Insulin Human Winthrop Comb 30 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 30 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 30, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 30

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 30 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 30 (a biphasic isophane insulin suspension with 30% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 30 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 30 must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens:
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 30 next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, Insulin Human Winthrop Comb 30 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

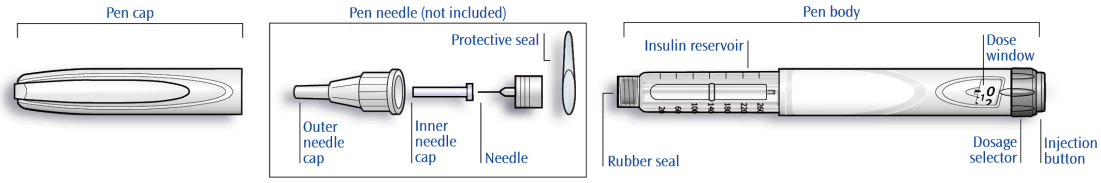
To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin suspensions (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures) should be mixed by turning SoloStar up and down at least 10 times to resuspend the insulin. The pen should be turned gently to avoid foaming in the cartridge. After mixing, the insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/163
EU/1/06/368/164
EU/1/06/368/165

EU/1/06/368/166
EU/1/06/368/167
EU/1/06/368/168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 50 is a biphasic isophane insulin suspension consisting of 50% dissolved insulin and 50% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 50 is injected subcutaneously 20 to 30 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 50 is administered subcutaneously. Insulin Human Winthrop Comb 50 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 50 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 50, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 50
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 50 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 50 (a biphasic isophane insulin suspension with 50% dissolved insulin) is an insulin with rapid onset and moderately long duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1.5 and 4 hours after injection and the duration of action is 12 to 16 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 50 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 50 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 50 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 50 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/047
EU/1/06/368/048

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 40 IU/ml suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 IU insulin human (equivalent to 1.4 mg) of the active substance.
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 50 is a biphasic isophane insulin suspension consisting of 50% dissolved insulin and 50% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 50 is injected subcutaneously 20 to 30 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insulin Human Winthrop Comb 50 is administered subcutaneously. Insulin Human Winthrop Comb 50 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 50 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 50, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 50
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 50 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 50 (a biphasic isophane insulin suspension with 50% dissolved insulin) is an insulin with rapid onset and moderately long duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1.5 and 4 hours after injection and the duration of action is 12 to 16 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 50 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 50 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 50 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 50 may be mixed with all insulin human formulations, but notwith those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/009
EU/1/06/368/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 50 is a biphasic isophane insulin suspension consisting of 50% dissolved insulin and 50% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a cartridge.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 50 is injected subcutaneously 20 to 30 minutes before a meal.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insulin Human Winthrop Comb 50 is administered subcutaneously. Insulin Human Winthrop Comb 50 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 50 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 50, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 50
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.
The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insulin Human Winthrop Comb 50 cartridges
The Insulin Human Winthrop Comb 50 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insulin Human Winthrop Comb 50 in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24 and AllStar which all deliver Insulin Human Winthrop Comb 50 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Not all of these pens may be marketed in your country.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 50 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,

- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 50 (a biphasic isophane insulin suspension with 50% dissolved insulin) is an insulin with rapid onset and moderately long duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1.5 and 4 hours after injection and the duration of action is 12 to 16 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 50 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 50 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insulin Human Winthrop Comb 50 must also not be mixed with insulins of animal origin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge
The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insulin pen
The Insulin Human Winthrop Comb 50 cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar or JuniorSTAR (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the suspension may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Cartridges
Before insertion into the pen, Insulin Human Winthrop Comb 50 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new

cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insulin Human Winthrop Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insulin Human Winthrop Comb 50 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

Insulin Human Winthrop Comb 50 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/092
EU/1/06/368/049
EU/1/06/368/050
EU/1/06/368/097
EU/1/06/368/102
EU/1/06/368/051

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Comb 50 is a biphasic isophane insulin suspension consisting of 50% dissolved insulin and 50% crystalline protamine insulin.

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insulin Human Winthrop Comb 50 is injected subcutaneously 20 to 30 minutes before a meal.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Comb 50 is administered subcutaneously. Insulin Human Winthrop Comb 50 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Comb 50 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Comb 50, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Comb 50

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Comb 50 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Comb 50 (a biphasic isophane insulin suspension with 50% dissolved insulin) is an insulin with rapid onset and moderately long duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1.5 and 4 hours after injection and the duration of action is 12 to 16 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Comb 50 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Comb 50 must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, Insulin Human Winthrop Comb 50 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insulin Human Winthrop Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.
Empty pens must never be re-used and must be properly discarded.

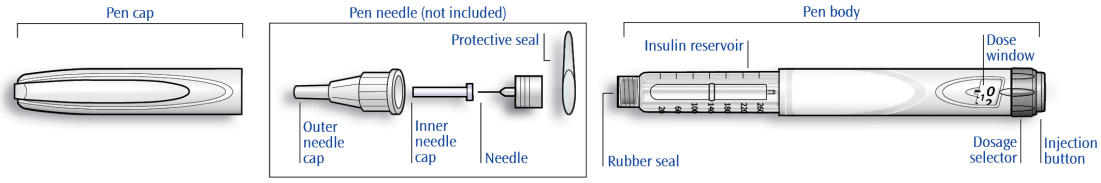
To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1. Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used.

After removing the pen cap, the appearance of the insulin should also be checked:
The insulin suspensions (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures) should be mixed by turning SoloStar up and down at least 10 times to resuspend the insulin. The pen should be turned gently to avoid foaming in the cartridge. After mixing, the insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

Only needles that are compatible for use with SoloStar should be used.

A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3. Perform a safety test

Prior to each injection, a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

Select a dose of 2 units.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4. Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show "0" following the safety test. The dose can then be selected.

Step 5. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6. Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles mut not be re-used.

Special caution must be taken when removing and disposing of the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/137
EU/1/06/368/138
EU/1/06/368/139

EU/1/06/368/140
EU/1/06/368/141
EU/1/06/368/142

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 10 ml of solution for injection, equivalent to 1000 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Infusat is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a vial.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
Insulin Human Winthrop Infusat has been specially designed for use in external portable insulin pumps. It is specially stabilised to minimise loss of efficacy which may result from mechanical and thermal stress in such pumps. Insulin Human Winthrop Infusat is therefore also suitable for continuous insulin infusion with other, conventional injection syringe pumps.

The desired blood glucose levels and the insulin dose regimen must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
When used in external portable insulin pumps, part of the daily insulin dose is infused continuously ("basal rate"), and the rest is administered in the form of bolus injections before meals. Refer to the operating instructions for detailed information about the infusion pump, its functions and the necessary safety precautions.

There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Consequently, about 40% to 60% of the daily dose is administered at a basal rate, and the rest is given as bolus injections before meals.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,

- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

Insulin Human Winthrop Infusat may be infused by the subcutaneous route. It is designed for use in the Hoechst Infusor and H-Tron insulin pumps. It may also be used in other insulin pumps for which it has been shown that they are suitable for this insulin (see pump manual). Only tetrafluoroethylene or polyethylene catheters must be used. Insulin Human Winthrop Infusat must not be used in peristaltic pumps with silicone tubing.

Insulin must always be infused under aseptic conditions. This is facilitated by the special equipment available for the insulin pumps (e.g. catheters, cannulas).

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). The puncture site within a given injection area must be changed regularly (generally, every 1 to 3 days).

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Infusat for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Infusat, since they may experience immunological cross-reactions.

In case of hypoglycaemia, the insulin pump should temporarily be turned off, at least until the patient has recovered complete consciousness.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Infusat

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,

- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Insulin pump faults
Hyperglycaemia, ketoacidosis and coma may develop within hours if the pump catheter is obstructed completely. Whenever the patient notices a rapid increase in blood glucose which does not respond to a bolus dose, a check must be made for possible catheter obstruction.

In the event of a pump malfunction, patients must always have injection devices (injection syringe or pen) and insulin available for subcutaneous injection. For details on safety precautions in the use of insulin pumps, refer to the operator's manual.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Infusat is an insulin with rapid onset and short duration of action.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol,
zinc chloride,
trometamol,
poloxamer 171,
glycerol,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Infusat must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Infusat must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Insulin that has been filled into the pump reservoir may be used for two weeks thereafter.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Infusat next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 3 vials are available.

6.6 Special precautions for disposal and other handling

Insulin Human Winthrop Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

For use in an infusion pump, Insulin Human Winthrop Infusat is filled into the sterile cartridge of the pump. The cartridge must only be used once.

Before use, the filled cartridge must be kept at room temperature for 1 to 2 hours. Air bubbles must be removed before starting the infusion (see the operator's manual for the pump).

If the infusion pump malfunctions, the solution may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Insulin Human Winthrop Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/056

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3.15 ml of solution for injection, equivalent to 315 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insulin Human Winthrop Infusat is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in *Escherichia coli.*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
Insulin Human Winthrop Infusat has been specially designed for use in external portable insulin pumps. It is specially stabilised to minimise loss of efficacy which may result from mechanical and thermal stress in such pumps. Insulin Human Winthrop Infusat is therefore also suitable for continuous insulin infusion with other, conventional injection syringe pumps.

The desired blood glucose levels and the insulin dose regimen must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
When used in external portable insulin pumps, part of the daily insulin dose is infused continuously ("basal rate"), and the rest is administered in the form of bolus injections before meals. Refer to the operating instructions for detailed information about the infusion pump, its functions and the necessary safety precautions.

There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Consequently, about 40% to 60% of the daily dose is administered at a basal rate, and the rest is given as bolus injections before meals.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,

- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population (≧65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration

Insulin Human Winthrop Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

Insulin Human Winthrop Infusat in cartridges may be infused by the subcutaneous route. It is designed for use in the Hoechst Infusor and H-Tron insulin pumps. It may also be used in other insulin pumps for which it has been shown that they are suitable for this insulin and this type of cartridge (see pump manual). Only tetrafluoroethylene or polyethylene catheters must be used.

Insulin must always be infused under aseptic conditions. This is facilitated by the special equipment available for the insulin pumps (e.g. catheters, cannulas).

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). The puncture site within a given injection area must be changed regularly (generally, every 1 to 3 days).

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients hypersensitive to Insulin Human Winthrop Infusat for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insulin Human Winthrop Infusat, since they may experience immunological cross-reactions.

In case of hypoglycaemia, the insulin pump should temporarily be turned off, at least until the patient has recovered complete consciousness.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insulin Human Winthrop Infusat

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,

- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Insulin pump faults
Hyperglycaemia, ketoacidosis and coma may develop within hours if the pump catheter is obstructed completely. Whenever the patient notices a rapid increase in blood glucose which does not respond to a bolus dose, a check must be made for possible catheter obstruction.

In the event of a pump malfunction, patients must always have injection devices (injection syringe or pen) and insulin available for subcutaneous injection. For details on safety precautions in the use of insulin pumps, refer to the operator's manual.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insulin Human Winthrop formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insulin Human Winthrop with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Human Winthrop is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies from controlled clinical studies are available. Insulin does cross the placental barrier, although not in clinically significant amount. A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin human indicates no safety issues in use of insulin human in pregnancy. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insulin Human Winthrop Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.
Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insulin Human Winthrop Infusat is an insulin with rapid onset and short duration of action.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol,
zinc chloride,
trometamol,
poloxamer 171,

glycerol,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insulin Human Winthrop Infusat must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insulin Human Winthrop Infusat must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge
The product (cartridges in-use in the pump) may be stored for a maximum of 2 weeks.

6.4 Special precautions for storage

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insulin Human Winthrop Infusat next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3.15 ml solution in a cartridge (type 1 colourless glass) with a plunger (fluoropolymer coated rubber (type 1, mixture of chlorobutyl and natural rubber)), a flanged cap (aluminium) and a stopper with hole (bromobutyl rubber (type 1), a Luer cone attachment (colourless polyethylene) and a Luer cap (colourless polyethylene).
Packs of 5 cartridges are available.

6.6 Special precautions for disposal and other handling

Insulin Human Winthrop Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Before use, Insulin Human Winthrop Infusat must be kept at room temperature for 1 to 2 hours. Air bubbles must be removed before starting the infusion (see the operator's manual for the pump).

If the infusion pump malfunctions, the solution may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Insulin Human Winthrop Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/057

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Brüningstraße 50
D-65926 Frankfurt / Main
Germany

Name and address of the manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Brüningstraße 50
D-65926 Frankfurt / Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a vial.

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/011 (1 vial of 5 ml)
EU/1/06/368/012 (5 vials of 5 ml)
EU/1/06/368/169 (1 vial of 10 ml)
EU/1/06/368/170 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Rapid

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Rapid 100 IU/ml solution for injection.

Insulin human

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 40 IU/ml solution for injection in a vial.

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/001 (1 vial of 10 ml)
EU/1/06/368/002 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Rapid

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Rapid 40 IU/ml solution for injection.

Insulin human

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGES

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a cartridge.

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
The Insulin Human Winthrop Rapid cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/088 (3 cartridges of 3 ml)
EU/1/06/368/013 (4 cartridges of 3 ml)
EU/1/06/368/014 (5 cartridges of 3 ml)
EU/1/06/368/093 (6 cartridges of 3 ml)
EU/1/06/368/098 (9 cartridges of 3 ml)
EU/1/06/368/015 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Rapid

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Rapid 100 IU/ml solution for injection.

Insulin human

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Rapid SoloStar 100 IU/ml solution for injection in a pre-filled pen

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/113 (3 pens of 3 ml)
EU/1/06/368/114 (4 pens of 3 ml)
EU/1/06/368/115 (5 pens of 3 ml)
EU/1/06/368/116 (6 pens of 3 ml)
EU/1/06/368/117 (9 pens of 3 ml)
EU/1/06/368/118 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Rapid SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Rapid SoloStar 100 IU/ml solution for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/020 (1 vial of 5 ml)
EU/1/06/368/021 (5 vials of 5 ml)
EU/1/06/368/171 (1 vial of 10 ml)
EU/1/06/368/172 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Basal

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Basal 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 40 IU/ml suspension for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/003 (1 vial of 10 ml)
EU/1/06/368/004 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Basal

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Basal 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS/3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a cartridge

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insulin Human Winthrop Basal cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/089 (3 cartridges of 3 ml)
EU/1/06/368/022 (4 cartridges of 3 ml)
EU/1/06/368/023 (5 cartridges of 3 ml)
EU/1/06/368/094 (6 cartridges of 3 ml)
EU/1/06/368/099 (9 cartridges of 3 ml)
EU/1/06/368/024 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Basal

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Basal 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/119 (3 pens of 3 ml)
EU/1/06/368/120 (4 pens of 3 ml)
EU/1/06/368/121(5 pens of 3 ml)
EU/1/06/368/122 (6 pens of 3 ml)
EU/1/06/368/123 (9 pens of 3 ml)
EU/1/06/368/124 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Basal SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Basal SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a vial

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/029 (1 vial of 5 ml)
EU/1/06/368/030 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 15

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 40 IU/ml suspension for injection in a vial

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/005 (1 vial of 10 ml)
EU/1/06/368/006 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 15

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 15 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a cartridge

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insulin Human Winthrop Comb 15 cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/090 (3 cartridges of 3 ml)
EU/1/06/368/031 (4 cartridges of 3 ml)
EU/1/06/368/032 (5 cartridges of 3 ml)
EU/1/06/368/095 (6 cartridges of 3 ml)
EU/1/06/368/100 (9 cartridges of 3 ml)
EU/1/06/368/033 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 15

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/125 (3 pens of 3 ml)
EU/1/06/368/126 (4 pens of 3 ml)
EU/1/06/368/127 (5 pens of 3 ml)
EU/1/06/368/128 (6 pens of 3 ml)
EU/1/06/368/129 (9 pens of 3 ml)
EU/1/06/368/130 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 15 SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 15 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a vial

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/038 (1 vial of 5 ml)
EU/1/06/368/039 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 25

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 40 IU/ml suspension for injection in a vial

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/007 (1 vial of 10 ml)
EU/1/06/368/008 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 25

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 25 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a cartridge

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insulin Human Winthrop Comb 25 cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/091 (3 cartridges of 3 ml)
EU/1/06/368/040 (4 cartridges of 3 ml)
EU/1/06/368/041 (5 cartridges of 3 ml)
EU/1/06/368/096 (6 cartridges of 3 ml)
EU/1/06/368/101 (9 cartridges of 3 ml)
EU/1/06/368/042 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 25

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/131 (3 pens of 3 ml)
EU/1/06/368/132 (4 pens of 3 ml)
EU/1/06/368/133 (5 pens of 3 ml)
EU/1/06/368/134 (6 pens of 3 ml)
EU/1/06/368/135 (9 pens of 3 ml)
EU/1/06/368/136 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 25 SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 25 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a vial

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/143 (1 vial of 5 ml)
EU/1/06/368/144 (5 vials of 5 ml)
EU/1/06/368/173 (1 vial of 10 ml)
EU/1/06/368/174 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 30

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a cartridge

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insulin Human Winthrop Comb 30 cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24,AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/145 (3 cartridges of 3 ml)
EU/1/06/368/146 (4 cartridges of 3 ml)
EU/1/06/368/147 (5 cartridges of 3 ml)
EU/1/06/368/148 (6 cartridges of 3 ml)
EU/1/06/368/149 (9 cartridges of 3 ml)
EU/1/06/368/150 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 30

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/163 (3 pens of 3 ml)
EU/1/06/368/164 (4 pens of 3 ml)
EU/1/06/368/165 (5 pens of 3 ml)
EU/1/06/368/166 (6 pens of 3 ml)
EU/1/06/368/167 (9 pens of 3 ml)
EU/1/06/368/168 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 30 SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 30 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a vial

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/047 (1 vial of 5 ml)
EU/1/06/368/048 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 50

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 40 IU/ml suspension for injection in a vial

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a vial.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/009 (1 vial of 10 ml)
EU/1/06/368/010 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 50

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 50 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a cartridge

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a cartridge.
3 cartridges of 3 ml
4 cartridges of 3 ml
5 cartridges of 3 ml
6 cartridges of 3 ml
9 cartridges of 3 ml
10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insulin Human Winthrop Comb 50 cartridges are to be used only with the pens: OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar, JuniorSTAR.
Not all of these pens may be marketed in your country.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/092 (3 cartridges of 3 ml)
EU/1/06/368/049 (4 cartridges of 3 ml)
EU/1/06/368/050 (5 cartridges of 3 ml)
EU/1/06/368/097 (6 cartridges of 3 ml)
EU/1/06/368/102 (9 cartridges of 3 ml)
EU/1/06/368/051 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 50

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Comb 50 SoloStar 100 IU/ml suspension for injection in a pre-filled pen.

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled pen.
3 pens of 3 ml
4 pens of 3 ml
5 pens of 3 ml
6 pens of 3 ml
9 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/137 (3 pens of 3 ml)
EU/1/06/368/138 (4 pens of 3 ml)
EU/1/06/368/139 (5 pens of 3 ml)
EU/1/06/368/140 (6 pens of 3 ml)
EU/1/06/368/141 (9 pens of 3 ml)
EU/1/06/368/142 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Comb 50 SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Comb 50 SoloStar 100 IU/ml suspension for injection.

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 10 ML VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a vial.

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

3. LIST OF EXCIPIENTS

Excipients: phenol, zinc chloride, trometamol, glycerol, poloxamer 171, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial.
3 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use. For use in insulin pumps, which are suitable for insulins containing 100 IU/ml.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.

Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/056

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Infusat

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Infusat 100 IU/ml solution for injection.

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3.15 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a cartridge.

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

3. LIST OF EXCIPIENTS

Excipients: phenol, zinc chloride, trometamol, glycerol, poloxamer 171, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a cartridge.
5 cartridges of 3.15 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use. For use in insulin pumps, which are suitable for insulins containing 100 IU/ml.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.

Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/368/057

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Insulin Human Winthrop Infusat

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insulin Human Winthrop Infusat 100 IU/ml solution for injection.

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.15 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Insulin Human Winthrop Rapid is and what it is used for

Insulin Human Winthrop Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Rapid is an insulin solution with a rapid onset and short duration of action.

Insulin Human Winthrop Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insulin Human Winthrop Rapid may also be used for treating hyperglycaemic coma (coma caused by too much blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar) as well as for controlling blood sugar before, during and after surgery.

2. What you need to know before you use Insulin Human Winthrop Rapid

Do not use Insulin Human Winthrop Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Rapid.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),

- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insulin Human Winthrop Rapid is a solution for injection under the skin or, in exceptional circumstances, into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Insulin administration into a vein for example to treat severe hyperglycaemia and ketoacidosis, requires experience and special safety precautions. For these reasons, it must be done in a clinic or a similar setting.

Do not use Insulin Human Winthrop Rapid in insulin pumps – special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the vials

Insulin Human Winthrop Rapid contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Do not shake the vial vigorously as this could cause froth to form. Froth can make it difficult for you to measure the correct dose.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Rapid may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw Insulin Human Winthrop Rapid into the injection syringe before the other insulin. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Rapid than you should

- If you **have injected too much Insulin Human Winthrop Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Rapid

- If you **have missed a dose of Insulin Human Winthrop Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Rapid

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)

- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.

- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Rapid contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Rapid contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Rapid"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Rapid looks like and contents of the pack
Insulin Human Winthrop Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insulin Human Winthrop Rapid is supplied in vials containing 5 ml of solution for injection (equivalent to 500 IU) or 10 ml of solution for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma NorgeAS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Rapid 40 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Rapid is and what it is used for

Insulin Human Winthrop Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Rapid is an insulin solution with a rapid onset and short duration of action.

Insulin Human Winthrop Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insulin Human Winthrop Rapid may also be used for treating hyperglycaemic coma (coma caused by too much blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar) as well as for controlling blood sugar before, during and after surgery.

2. What you need to know before you use Insulin Human Winthrop Rapid

Do not use Insulin Human Winthrop Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Rapid.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Rapid alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast--eeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insulin Human Winthrop Rapid is a solution for injection under the skin or, in exceptional circumstances, into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Insulin administration into a vein for example to treat severe hyperglycaemia and ketoacidosis, requires experience and special safety precautions. For these reasons, it must be done in a clinic or a similar setting.

Do not use Insulin Human Winthrop Rapid in insulin pumps – special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the vials

Insulin Human Winthrop Rapid contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Insulin Human Winthrop Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Do not shake the vial vigorously as this could cause froth to form. Froth can make it difficult for you to measure the correct dose.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Rapid may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw Insulin Human Winthrop Rapid into the injection syringe before the other insulin. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Rapid than you should

- If you **have injected too much Insulin Human Winthrop Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Rapid

- If you **have missed a dose of Insulin Human Winthrop Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Rapid

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannnot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)

- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.

- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp) Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Rapid contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Rapid contains 40 IU (International Units) of the active substance insulin human.
- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of

Insulin Human Winthrop Rapid"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Rapid looks like and contents of the pack
Insulin Human Winthrop Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insulin Human Winthrop Rapid is supplied in vials containing 10 ml solution (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid ").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid ").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Rapid is and what it is used for

Insulin Human Winthrop Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Rapid is an insulin solution with a rapid onset and short duration of action.

Insulin Human Winthrop Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insulin Human Winthrop Rapid may also be used for treating hyperglycaemic coma (coma caused by too much blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar) as well as for controlling blood sugar before, during and after surgery.

2. What you need to know before you use Insulin Human Winthrop Rapid

Do not use Insulin Human Winthrop Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Rapid.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Oher medicines and Insulin Human Winthrop Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),

- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insulin Human Winthrop Rapid is a solution for injection under the skin or, in exceptional circumstances, into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Insulin administration into a vein for example to treat severe hyperglycaemia and ketoacidosis, requires experience and special safety precautions. For these reasons, it must be done in a clinic or a similar setting.

Do not use Insulin Human Winthrop Rapid in insulin pumps - special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Rapid cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.

Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen.

Look at the cartridge before you use it. Only use it if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.

- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Rapid than you should
- If you **have injected too much Insulin Human Winthrop Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Rapid
- If you **have missed a dose of Insulin Human Winthrop Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Rapid

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Rapid next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Rapid contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Rapid contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Rapid"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Rapid looks like and contents of the pack
Insulin Human Winthrop Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insulin Human Winthrop Rapid is supplied in cartridges containing 3 ml solution (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,

- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in

concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Rapid SoloStar 100 IU/ml, solution for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Winthrop Rapid SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Rapid is and what it is used for

Insulin Human Winthrop Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Rapid is an insulin solution with a rapid onset and short duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Rapid

Do not use Insulin Human Winthrop Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Rapid.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insulin Human Winthrop Rapid is a solution for injection under the skin.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Look at the cartridge before you use the pen. Do not use Insulin Human Winthrop Rapid if you notice particles in it. Only use Insulin Human Winthrop Rapid if the solution is clear, colourless and waterlike.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Rapid SoloStar pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Rapid than you should
- If you **have injected too much Insulin Human Winthrop Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Rapid
- If you **have missed a dose of Insulin Human Winthrop Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Rapid

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency annot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Rapid contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Rapid contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Rapid"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Rapid looks like and contents of the pack
Insulin Human Winthrop Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insulin Human Winthrop Rapid is supplied in pre-filled pens, SoloStar, containing 3 ml solution (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Rapid SoloStar solution for injection in a pre-filled pen. Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

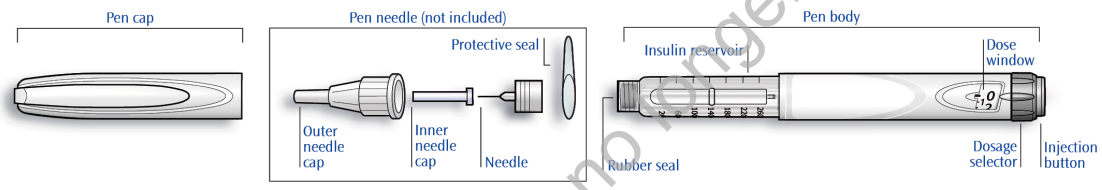
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

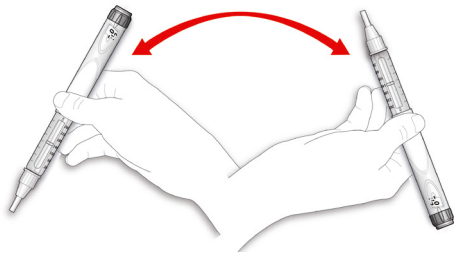
Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.

If you are using clear insulin (Insulin Human Winthrop Rapid), do not use this pen if the insulin is cloudy, coloured or has particles.



Step 2. Attach the needle

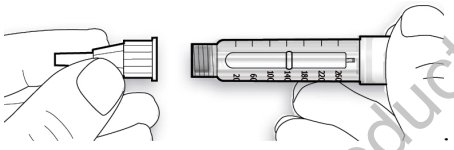
Always use a new sterile needle for each injection. This helps prevent contamination and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

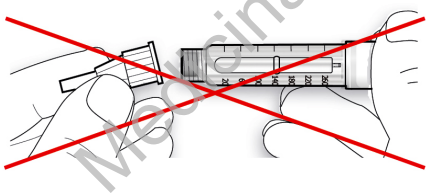
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



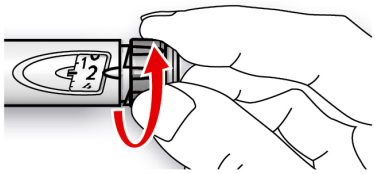
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



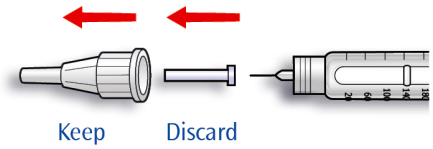
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



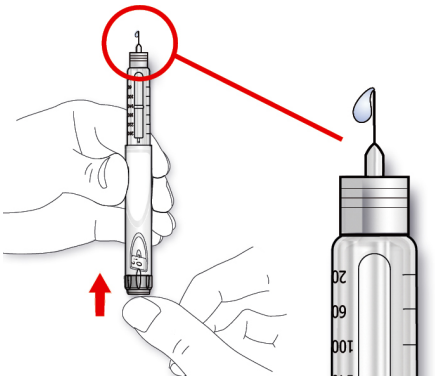
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

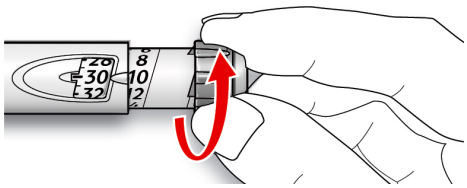
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



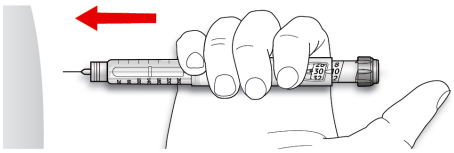
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

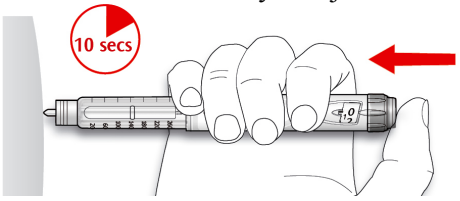
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Basal is and what it is used for

Insulin Human Winthrop Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insulin Human Winthrop Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Basal

Do not use Insulin Human Winthrop Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Basal
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insulin Human Winthrop Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Basal contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Basal may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Basal. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Basal than you should

- If you **have injected too much Insulin Human Winthrop Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Basal

- If you **have missed a dose of Insulin Human Winthrop Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Basal

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Basal contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Basal looks like and contents of the pack
After mixing, Insulin Human Winthrop Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Basal is supplied in vials containing 5 ml of suspension for injection (500 IU) or 10 ml of suspension for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Basal 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Basal is and what it is used for

Insulin Human Winthrop Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insulin Human Winthrop Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Basal

Do not use Insulin Human Winthrop Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Basal.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early**.

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insulin Human Winthrop Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Basal contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Basal may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Basal. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Basal than you should

- If you **have injected too much Insulin Human Winthrop Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Basal

- If you **have missed a dose of Insulin Human Winthrop Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Basal

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)

- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.

- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Basal contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Basal contains 40 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important

information about some of the ingredients of Insulin Human Winthrop Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Basal looks like and contents of the pack
After mixing, Insulin Human Winthrop Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Basal is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Basal is and what it is used for

Insulin Human Winthrop Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insulin Human Winthrop Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Basal

Do not use Insulin Human Winthrop Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Basal.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Basal with alcohol.

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insulin Human Winthrop Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Basal cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.

Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Basal than you should
- If you have **injected too much Insulin Human Winthrop Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Hun Winthrop Basal
- If you have **missed a dose of Insulin Human Winthrop Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

<u>Unopened cartridges</u>
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Basal next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

<u>In-use cartridges</u>
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Basal contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Basal looks like and contents of the pack
After mixing, Insulin Human Winthrop Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Basal is supplied in cartridges containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Human Winthrop Basal SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Basal is and what it is used for

Insulin Human Winthrop Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Basal

Do not use Insulin Human Winthrop Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Basal
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insulin Human Winthrop Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Basal into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Basal SoloStar pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Basal than you should
- If you **have injected too much Insulin Human Winthrop Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Basal
- If you **have missed a dose of Insulin Human Winthrop Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Basal contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Basal looks like and contents of the pack
After mixing, Insulin Human Winthrop Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Basal is supplied in pre-filled pens, SoloStar, containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,

- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in

concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Basal SoloStar suspension for injection in a pre-filled pen.
Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

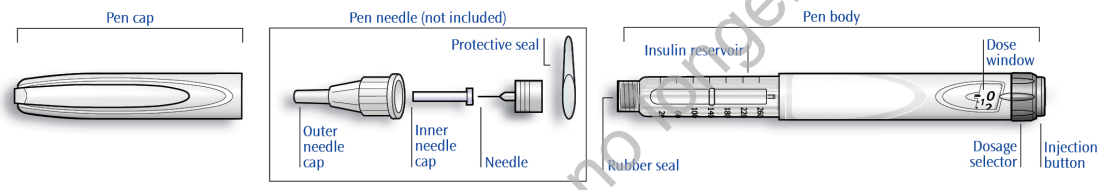
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

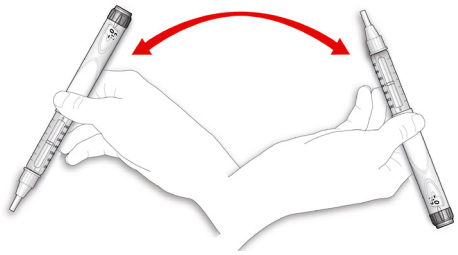
Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.

If you are using a suspension insulin (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

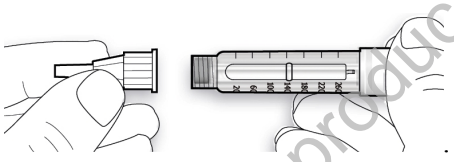
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

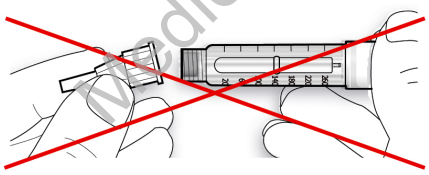
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



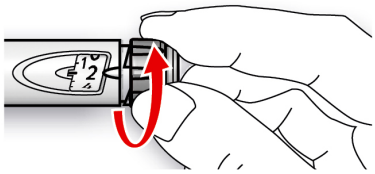
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



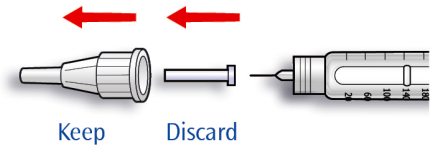
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



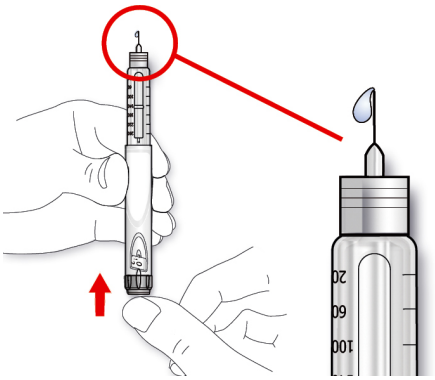
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

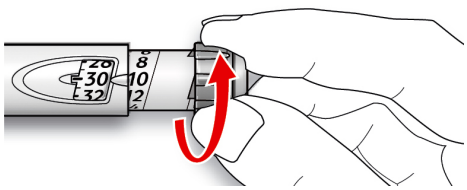
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



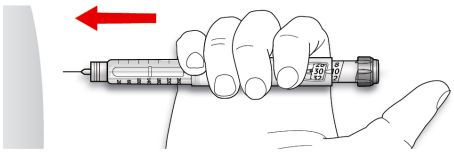
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

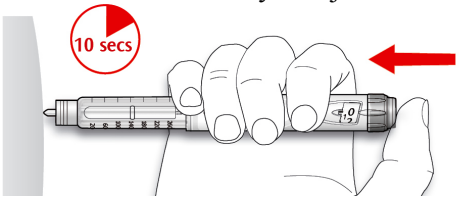
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 15 is and what it is used for

Insulin Human Winthrop Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 15 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 15

Do not use Insulin Human Winthrop Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to you doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 15.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 15 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 15 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 15 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 15. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 15 than you should

- If you **have injected too much Insulin Human Winthrop Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 15

- If you **have missed a dose of Insulin Human Winthrop Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 15

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP" and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 15 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 15"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 15 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 15 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 15 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 15 is and what it is used for

Insulin Human Winthrop Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 15 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 15

Do not use Insulin Human Winthrop Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 15.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 15 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 15 contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off capon the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 15 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 15. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 15 than you should

- If you **have injected too much Insulin Human Winthrop Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 15

- If you **have missed a dose of Insulin Human Winthrop Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 15

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 15 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 15 contains 40 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 15"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 15 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 15 is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15.").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 15 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 15 is and what it is used for

Insulin Human Winthrop Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 15 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 15

Do not use Insulin Human Winthrop Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 15.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling,-consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Oother medicines and Insulin Human Winthrop Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 15 into a vein (blodd vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Comb 15 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge must also be used if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Comb 15 than you should
- If you **have injected too much Insulin Human Winthrop Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 15
- If you **have missed a dose of Insulin Human Winthrop Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 15
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 15 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 15 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 "Important information about some of the ingredients of Insulin Human Winthrop Comb 15"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 15 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 15 is a uniformly milky-fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 15 is supplied in cartridges containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop comb 15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Human Winthrop Comb 15 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 15 is and what it is used for

Insulin Human Winthrop Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 15 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 15

Do not use Insulin Human Winthrop Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 15.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby..

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 15 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Comb 15 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Comb 15 than you should

- If you **have injected too much Insulin Human Winthrop Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 15

- If you **have missed a dose of Insulin Human Winthrop Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 15

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not know). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 15 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 15"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 15 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 15 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Comb 15 SoloStar suspension for injection in a pre-filled pen.
Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

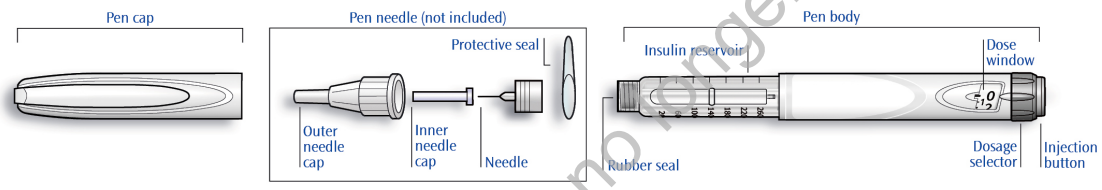
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

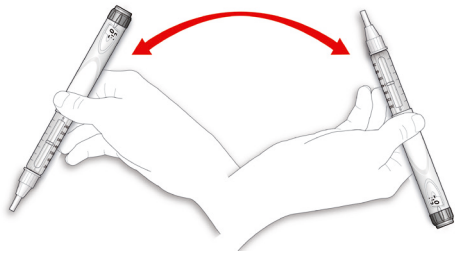
Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.

If you are using a suspension insulin (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

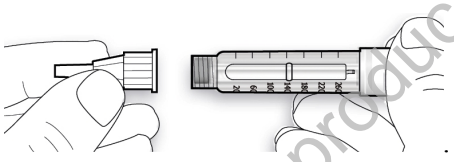
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

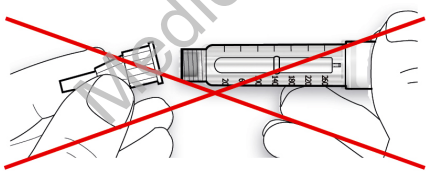
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



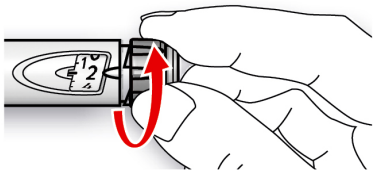
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



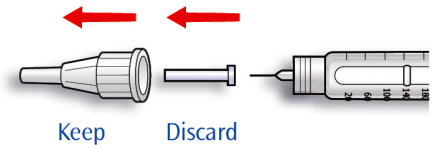
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



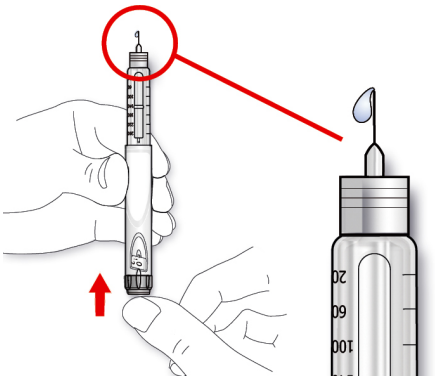
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

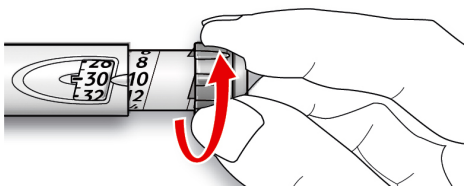
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



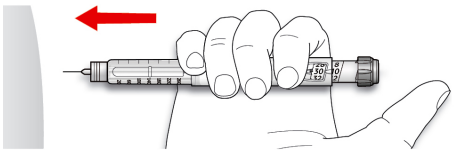
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

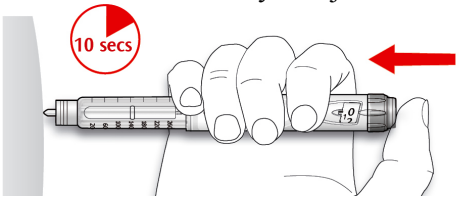
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 25 is and what it is used for

Insulin Human Winthrop Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 25

Do not use Insulin Human Winthrop Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 25.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 25 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial must also be used if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicine except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 25 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 25. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 25 than you should

- If you **have injected too much Insulin Human Winthrop Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 25

- If you **have missed a dose of Insulin Human Winthrop Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 25

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 25 and other insulins.

4. Possible side effects

Like all medicines, Insulin Human Winthrop Comb 25 can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions caanot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 25 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 25 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 25 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 25 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 25 is and what it is used for

Insulin Human Winthrop Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 25

Do not use Insulin Human Winthrop Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 25.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 25 alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 25 contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial must also be used if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 25 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 25. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 25 than you should

- If you **have injected too much Insulin Human Winthrop Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin HumaWinthrop Comb 25

- If you **have missed a dose of Insulin Human Winthrop Comb 25** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 25

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from availabla data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 25 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 25 contains 40 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 25 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 25 is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 25 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 25 is and what it is used for

Insulin Human Winthrop Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 25

Do not use Insulin Human Winthrop Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 25.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Comb 25 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.

Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Comb 25 than you should
- If you **have injected too much Insulin Human Winthrop Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 25
- If you **have missed a dose of Insulin Human Winthrop Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 25 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 25 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 25 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 25 is supplied in cartridge containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Human Winthrop Comb 25 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse? This includes any possible side effects not listed in this leaflet,.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 25 is and what it is used for

Insulin Human Winthrop Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 25 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 25

Do not use Insulin Human Winthrop Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 25.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 25 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Comb 25 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Comb 25 than you should
- If you **have injected too much Insulin Human Winthrop Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 25
- If you **have missed a dose of Insulin Human Winthrop Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 25 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 25 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 25 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Comb 25 Solostar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

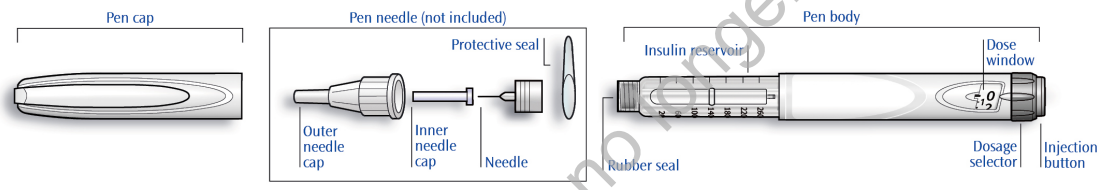
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

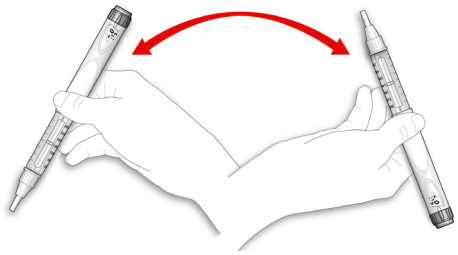
Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.

If you are using a suspension insulin (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

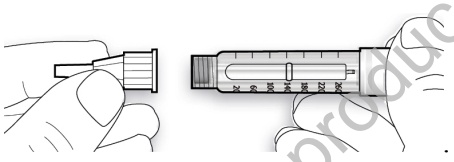
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

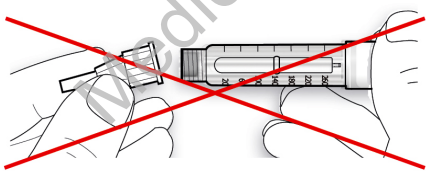
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



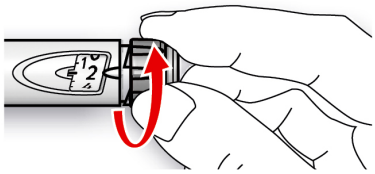
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



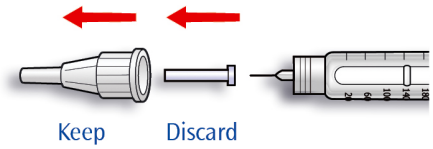
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



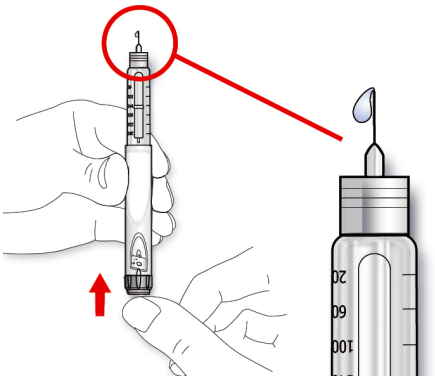
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

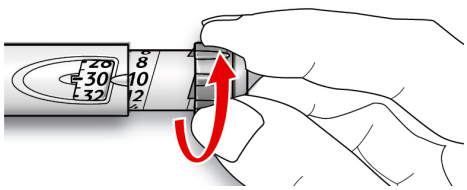
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



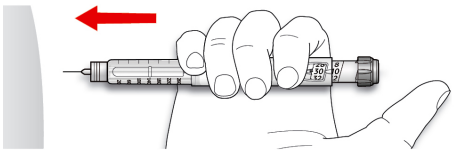
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

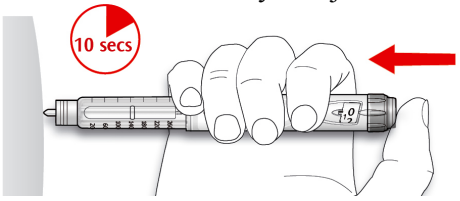
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 30 is and what it is used for

Insulin Human Winthrop Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 30 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 30

Do not use Insulin Human Winthrop Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 30.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 30 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 30 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial must also be used if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 30 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 30. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 30 than you should

- If you **have injected too much Insulin Human Winthrop Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 30

- If you **have missed a dose of Insulin Human Winthrop Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 30

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 30 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 30 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 30"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 30 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 30 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 30 is supplied in vials containing 5 ml of suspension for injection (equivalent to 500 IU) or 10 ml of suspension for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 30 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 30 is and what it is used for

Insulin Human Winthrop Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 30 is an insulin preparation with a gradual onset and long duration of action.

Insulin Human Winthrop Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 30

Do not use Insulin Human Winthrop Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 30.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 30 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Comb 30 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.

Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Comb 30 than you should
- If you **have injected too much Insulin Human Winthrop Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 30
- If you **have missed a dose of Insulin Human Winthrop Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 30
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 30 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 30 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 30"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 30 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 30 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 30 is supplied in cartridge containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Human Winthrop Comb 30 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 30 is and what it is used for

Insulin Human Winthrop Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 30 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 30

Do not use Insulin Human Winthrop Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 30.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 30 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Comb 30 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Comb 30 than you should
- If you **have injected too much Insulin Human Winthrop Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 30
- If you **have missed a dose of Insulin Human Winthrop Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 30
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 30 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 30"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 30 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 30is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 30 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

2. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Comb 30 SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

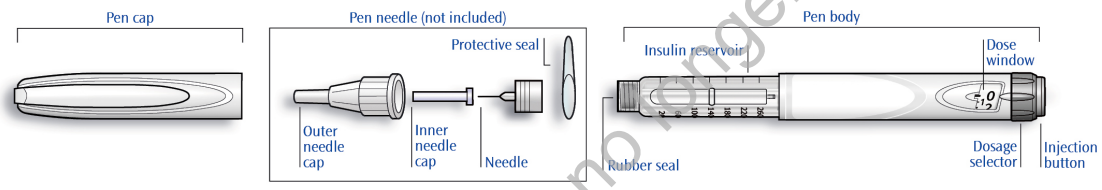
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurseor call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

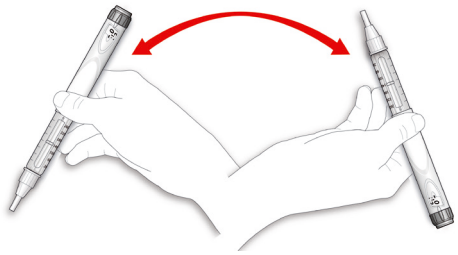
Step 1. Check the insulin

A Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B Take off the pen cap.

C Check the appearance of your insulin.

If you are using a suspension insulin (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

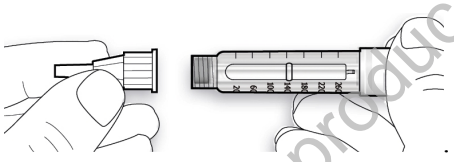
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

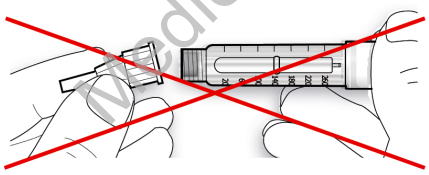
Please note: The needles shown are for illustrative purposes only.

A Remove the protective seal from a new needle.

B Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



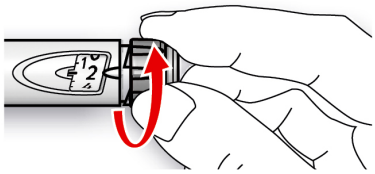
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



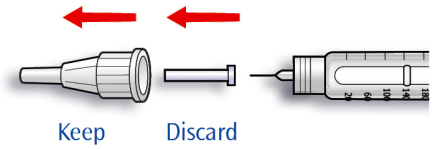
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A Select a dose of 2 units by turning the dosage selector.



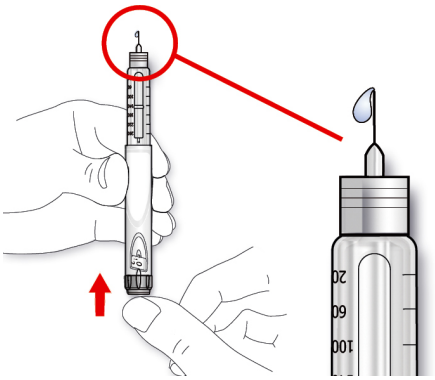
B Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C Hold the pen with the needle pointing upwards.

D Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

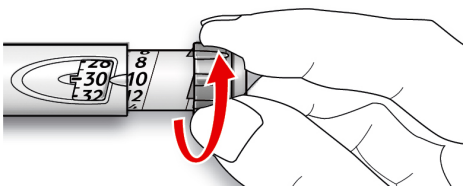
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A Check that the dose window shows “0” following the safety test.

B Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



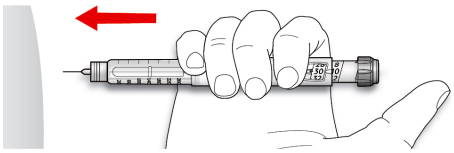
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

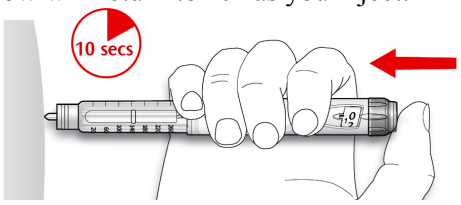
Step 5. Inject the dose

A Use the injection method as instructed by your doctor, pharmacist or nurse.

B Insert the needle into the skin.



C Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B Dispose of the needle safely.

C Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 50 is and what it is used for

Insulin Human Winthrop Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insulin Human Winthrop Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 50

Do not use Insulin Human Winthrop Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 50.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 50 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 50 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 50. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 50 than you should

- If you **have injected too much Insulin Human Winthrop Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 50

- If you **have missed a dose of Insulin Human Winthrop Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 50

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 100 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 50 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 50"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 50 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 50 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 50 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 50 is and what it is used for

Insulin Human Winthrop Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insulin Human Winthrop Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 50

Do not use Insulin Human Winthrop Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 50.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insulin Human Winthrop Comb 50 contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off cap on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insulin Human Winthrop Comb 50 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insulin Human Winthrop Comb 50. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insulin Human Winthrop Comb 50 than you should

- If you **have injected too much Insulin Human Winthrop Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 50

- If you **have missed a dose of Insulin Human Winthrop Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 50

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°Cand away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 50 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 50 contains 40 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 50"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 50 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 50 is supplied in vials contains 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 50 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 50 is and what it is used for

Insulin Human Winthrop Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insulin Human Winthrop Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin**.** Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 50

Do not use Insulin Human Winthrop Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Comb 50.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.
If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

To ensure you get the accurate dose, the Insulin Human Winthrop Comb 50 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- OptiPen, ClikSTAR, Tactipen, Autopen 24 or AllStar which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.
-
-

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Comb 50 than you should
- If you **have injected too much Insulin Human Winthrop Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin HumaWinthrop Comb 50
- If you **have missed a dose of Insulin Human Winthrop Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar).** The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood

pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Comb 50 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 50 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 50"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 50 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 50 is supplied in cartridges containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Comb 50 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully, including the Instructions for Use of Insulin Human Winthrop Comb 50 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Comb 50 is and what it is used for

Insulin Human Winthrop Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insulin Human Winthrop Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Comb 50

Do not use Insulin Human Winthrop Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse befor using Insulin Human Winthrop Comb 50.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insulin Human Winthrop Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Insulin Human Winthrop Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insulin Human Winthrop Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insulin Human Winthrop Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insulin Human Winthrop Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insulin Human Winthrop Comb 50 into a vein.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing human insulin.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.
A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Comb 50 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new SoloStar has to be used.

If you use more Insulin Human Winthrop Comb 50 than you should
- If you **have injected too much Insulin Human Winthrop Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Comb 50
- If you **have missed a dose of Insulin Human Winthrop Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 peopel)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which isstated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Comb 50 contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insulin Human Winthrop Comb 50"), hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Comb 50 looks like and contents of the pack
After mixing, Insulin Human Winthrop Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insulin Human Winthrop Comb 50 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Polska
sanofi-aventis Sp . z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, " Other medicines and Insulin Human Winthrop Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, " Other medicines and Insulin Human Winthrop Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, " Other medicines and Insulin Human Winthrop Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insulin Human Winthrop Comb 50 SoloStar suspension for injection in a pre-filled pen.
Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

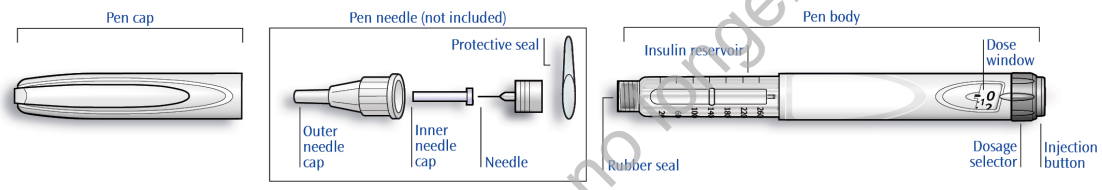
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

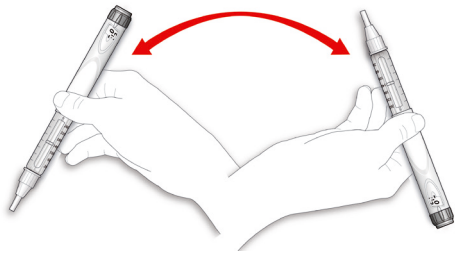
Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insulin Human Winthrop SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insulin Human Winthrop insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.

If you are using a suspension insulin (Insulin Human Winthrop Basal or Insulin Human Winthrop mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

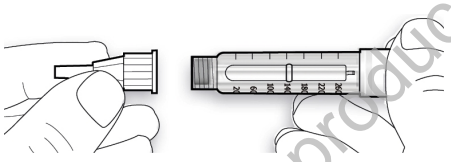
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

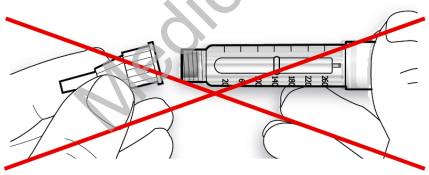
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



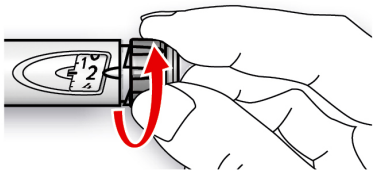
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



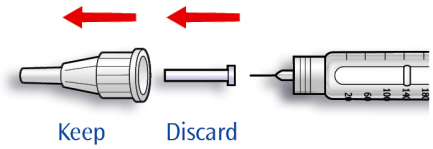
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



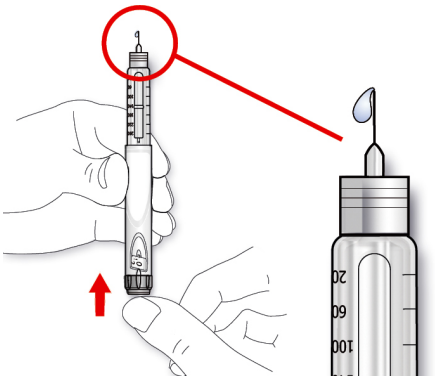
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

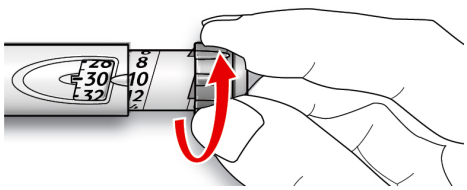
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



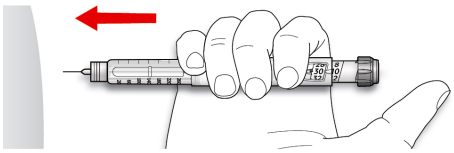
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

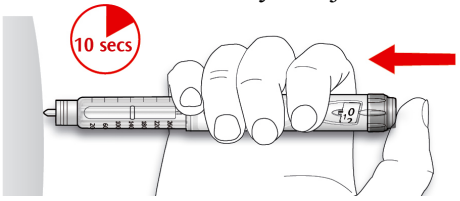
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Insulin Human Winthrop Infusat is and what it is used for

Insulin Human Winthrop Infusat contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Infusat is an insulin solution with a rapid onset and short duration of action.

Insulin Human Winthrop Infusat must only be used in insulin pumps suitable for this insulin.

Insulin Human Winthrop Infusat is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Infusat

Do not use Insulin Human Winthrop Infusat

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insulin Human Winthrop Infusat.
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- whom to contact in the event of technical problems with your pump,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Infusat

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Infusat with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

3. How to use Insulin Human Winthrop Infusat

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Infusat per day you will need, how much of this is infused continuously ("basal rate") and how much and when you need additional insulin as an "insulin boost" ("bolus dose"),
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to use a higher or lower dose of Insulin Human Winthrop Infusat.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Insulin Human Winthrop Infusat is a solution to be given under the skin.

Your doctor will show you how and in which area of the skin you should infuse your insulin and how often you must change the puncture site within the particular area of skin where you are infusing the insulin. Speak to your doctor before you change the area of skin that you are infusing.

Do not use Insulin Human Winthrop Infusat in peristaltic pumps with silicone tubing. Situations in which you must not start or continue to use insulin pumps are described in the operating manuals for these pumps.

How to handle the vials

Insulin Human Winthrop Infusat has been developed for use in Hoechst Infusor and H-Tron. It must only be used in insulin pumps suitable for this insulin. Only tetrafluoroethylene or polyethylene catheters must be used for infusion. The operating manual provided with the pump will tell you how to use it.

Insulin Human Winthrop Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

The insulin cartridge of the pump must be sterile and must be used once only. After filling the cartridge of the pump keep it at room temperature for 1 to 2 hours before using it, so that you can see and remove any air bubbles which form during warming-up.

Special care before injection

Before starting the infusion remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Infusat must NOT be mixed with any other insulin preparations.

Insulin pump faults

You should always consider the possibility of a technical problem if, in order to achieve the desired blood sugar levels,
- you need additional insulin ("bolus doses") at larger doses or more often than usual, or
- you need additional insulin ("bolus doses") at smaller doses or less often than usual.

For details on safety precautions in the use of insulin pumps see the operating manual.

If the pump does not function well, you can draw the insulin from the cartridge into an injection syringe for injection. Therefore, keep injection syringes and injection needles as well. However, use

only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Infusat than you should
- If you **have injected too much Insulin Human Winthrop Infusat**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Infusat
- If you **have missed a dose of Insulin Human Winthrop Infusat** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Infusat
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Infusat without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Infusat and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Infusat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial afetr "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Infusat next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Once in the pump, Insulin Human Winthrop Infusat may be kept for up to 2 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Infusat contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Infusat contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: phenol, zinc chloride, trometamol, poloxamer 171, glycerol, hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Infusat looks like and contents of the pack
Insulin Human Winthrop Infusat is a clear, colourless solution for injection, with no solid particles visible, and of water-like consistency.

Insulin Human Winthrop Infusat is supplied in vials containing 10 ml solution (1000 IU). Pack of 3 vials of 10 ml is available.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pump does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Stop your insulin infusion (if necessary, by withdrawing the needle) at least until you feel that you are fully alert again. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Insulin Human Winthrop Infusat is and what it is used for

Insulin Human Winthrop Infusat contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insulin Human Winthrop Infusat is an insulin solution with a rapid onset and short duration of action. It comes in cartridges designed for use in Hoechst Infusor and H-Tron (insulin pumps).

Insulin Human Winthrop Infusat must only be used in insulin pumps suitable for this insulin.

Insulin Human Winthrop Infusat is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insulin Human Winthrop Infusat

Do not use Insulin Human Winthrop Infusat

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse beforing using Insulin Human Winthrop Infusat
Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- whom to contact in the event of technical problems with your pump,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insulin Human Winthrop Infusat

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),

- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Betablockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insulin Human Winthrop Infusat with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

3. How to use Insulin Human Winthrop Infusat

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insulin Human Winthrop Infusat per day you will need, how much of this is infused continuously ("basal rate") and how much and when you need additional insulin as an "insulin boost" ("bolus dose"),
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to use a higher or lower dose of Insulin Human Winthrop Infusat.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Insulin Human Winthrop Infusat is a solution to be given under the skin.

Your doctor will show you how and in which area of the skin you should infuse your insulin and how often you must change the puncture site within the particular area of skin where you are infusing the insulin. Speak to your doctor before you change the area of skin that you are infusing.

Do not use Insulin Human Winthrop Infusat in peristaltic pumps with silicone tubing. Situations in which you must not start or continue to use insulin pumps are described in the operating manuals for these pumps.

How to handle the cartridges

Insulin Human Winthrop Infusat comes in cartridges designed for use in Hoechst Infusor and H-Tron. It must only be used in insulin pumps suitable for this insulin. Only tetrafluoroethylene or polyethylene catheters must be used for infusion. The operating manual provided with the pump will tell you how to use it.

Insulin Human Winthrop Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Keep the cartridge at room temperature 1 to 2 hours before inserting it in the pump so that you can see and remove any air bubbles which form during warming-up.

Special care before injection

Before starting the infusion remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insulin Human Winthrop Infusat must NOT be mixed with any other insulin preparations.

Do not re-fill and re-use empty cartridges.

Insulin pump faults

You should always consider the possibility of a technical problem if, in order to achieve the desired blood sugar levels,
- you need additional insulin ("bolus doses") at larger doses or more often than usual, or
- you need additional insulin ("bolus doses") at smaller doses or less often than usual.

For details on safety precautions in the use of insulin pumps see the operating manual.

If the pump does not function well, you can draw the insulin from the cartridge into an injection syringe for injection. Therefore, keep injection syringes and injection needles as well. However, use

only those injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insulin Human Winthrop Infusat than you should
- If you **have injected too much Insulin Human Winthrop Infusat**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insulin Human Winthrop Infusat
- If you **have missed a dose of Insulin Human Winthrop Infusat** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Insulin Human Winthrop Infusat
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insulin Human Winthrop Infusat without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insulin Human Winthrop Infusat and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body); severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include (frequency cannot be estimated from the available data)
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Insulin Human Winthrop Infusat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insulin Human Winthrop Infusat next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

Once in the pump, Insulin Human Winthrop Infusat may be kept for up to 2 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insulin Human Winthrop Infusat contains
- The active substance is insulin human. One ml of Insulin Human Winthrop Infusat contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: phenol, zinc chloride, trometamol, poloxamer 171, glycerol, hydrochloric acid (for pH adjustment) and water for injections.

What Insulin Human Winthrop Infusat looks like and contents of the pack
Insulin Human Winthrop Infusat is a clear, colourless solution for injection, with no solid particles visible, and of water-like consistency.

Insulin Human Winthrop Infusat is supplied in cartridges containing 3.15 ml solution (315 IU). Pack of 5 cartridges of 3.15 ml is available.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
sanofi-aventis Bulgaria EOOD
Тел.: +359 (0)2 970 53 00

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0)180 20 200 10

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Lietuva
UAB «SANOFI-AVENTIS LIETUVA»
Tel: +370 5 2755224

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi Malta Ltd
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)182 557 755

Norge
Aventis Pharma Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Italia
Sanofi S.p.A.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pump does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insulin Human Winthrop,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insulin Human Winthrop Infusat").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing

can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Stop your insulin infusion (if necessary, by withdrawing the needle) at least until you feel that you are fully alert again. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.
