ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Monotard 40 IU/ml
Suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin human, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).

1 ml contains 40 IU of insulin human
1 vial contains 10 ml equivalent to 400 IU

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Monotard is an insulin zinc suspension. The suspension consists of a mixture of amorphous and crystalline particles (ratio 3:7).

For excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

Monotard is a cloudy, white, aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

Monotard is a long-acting insulin.

Dosage
Dosage is individual and determined by the physician in accordance with the needs of the patient. The average range of total daily insulin requirement for maintenance therapy in type 1 diabetic patients lies between 0.5 and 1.0 IU/kg. In pre-pubertal children it usually varies from 0.7 to 1.0 IU/kg. During the period of partial remission, the insulin requirements can be much lower, whereas in insulin resistant states e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher.

Initial dosages for type 2 diabetic patients are often lower, e.g. 0.3 to 0.6 IU/kg/day.

The physician determines whether one or several daily injections are necessary. Monotard may be used alone or mixed with fast-acting insulin. In intensive insulin therapy the suspension may be used as basal insulin (evening and/or morning injection) with fast-acting insulin given at meals.

In patients with diabetes mellitus optimised glycaemic control delays the onset and slows the progression of late diabetic complications. Blood glucose monitoring is therefore recommended.

Dosage adjustment
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.

Renal or hepatic impairment may reduce insulin requirement.

Adjustment of dosage may also be necessary if patients change physical activity or their usual diet. Dosage adjustment may be necessary when transferring patients from one insulin preparation to another (see section 4.4 Special warnings and special precautions for use).

Administration
For subcutaneous use.

Monotard is usually administered subcutaneously in the thigh. If convenient, the abdominal wall, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites.

Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.
Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.
Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Insulin suspensions are never to be administered intravenously.

Monotard is accompanied by a package leaflet with detailed instruction for use to be followed.

The vials are for use with insulin syringes with a corresponding unit scale.

4.3 Contraindications

Hypoglycaemia
Hypersensitivity to human insulin or to any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and special precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to **hyperglycaemia** and diabetic ketoacidosis.
Usually the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath (see section 4.8 Undesirable effects).
In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.
Hypoglycaemia can generally be corrected by immediate carbohydrate intake. In order to be able to take action immediately, patients should carry glucose with them at all times.
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly (see section 4.8 Undesirable effects).
Usual warning symptoms may disappear in patients with longstanding diabetes.
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), species (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a change in dosage.
If an adjustment is needed when switching the patients to Monotard, it may occur with the first dose or

during the first several weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.

Insulin suspensions are not to be used in insulin infusion pumps.

Monotard contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with the glucose metabolism. The physician must therefore take possible interactions into account and should always ask their patients about any medicinal products they take.

The following substances may reduce insulin requirement:
Oral hypoglycaemic agents (OHA), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates and alcohol.

The following substances may increase insulin requirement:
Thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide/ laneotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.
Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.
After delivery, insulin requirements return rapidly to pre-pregnancy values.

Insulin treatment of the nursing mother presents no risk to the baby. However, the Monotard dosage may need to be adjusted.

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. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
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 signs of

hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

The most often seen undesirable effect in insulin-treated patients is a change in blood glucose levels. **From clinical investigations it is known that major hypoglycaemia, defined as need for assistance in treatment, occurs in approximately 20% of well-controlled patients.** Based on post-marketing experience adverse drug reactions including hypoglycaemia have been reported rarely (>1/10,000 <1/1,000). The listings below are all based on post-marketing experience and is subject to underreporting and should be interpreted in that light.

Metabolism and nutrition disorders

Rare (>1/10,000 <1/1,000)	
Change in blood glucose	Hypoglycaemia: Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. Hyperglycaemia: Usually the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis which is potentially lethal. For precautions see section 4.4 Special warnings and special precautions for use.

Eye disorders

Very rare (<1/10,000)	Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

General disorders and administration site conditions

Very rare (<1/10,000)	Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.
Very rare (<1/10,000)	Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.
Very rare (<1/10,000)	Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Very rare (<1/10,000)	Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

4.9 Overdose

A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.
  Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiabetic agent. ATC code: A10A C01.

The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Monotard is a long-acting insulin.
Onset of action is within 2½ hours, reaches a maximum effect within 4-15 hours and the entire time of duration is approximately 24 hours.

5.2 Pharmacokinetic properties

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulins is therefore affected by significant intra- and inter-individual variation.

Absorption
The maximum plasma concentration of the insulins is reached within 2-18 hours after subcutaneous administration.

Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism
Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination
The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{½}$) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ of about 9-15 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride
Zinc acetate
Sodium chloride
Methyl parahydroxybenzoate
Sodium acetate
Sodium hydroxide or/and hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Insulin suspensions should not be added to infusion fluids.
Medicinal products added to the insulin suspension may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.
Mixing of Monotard with phosphate buffered insulin preparations is not recommended due to the risk of precipitation of zinc-phosphate, leading to an unpredictable timing of such insulin mixtures. When mixing Actrapid with Monotard immediate injection is necessary to avoid blunting of the fast acting effect of Actrapid.

6.3 Shelf life

30 months.

After first opening: 6 weeks.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator) not near a freezing compartment.
Do not freeze.
Keep the container in the outer carton in order to protect from light.

During use: do not refrigerate. Do not store above 25°C.

Protect from excessive heat and sunlight.

6.5 Nature and contents of container

Glass vial (type 1) closed with a bromobutyl/polyisoprene rubber stopper and a protective tamperproof plastic cap.
Pack sizes: 1 and 5 vials x 10 ml.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Insulin preparations, which have been frozen, must not be used.
Insulin suspensions should not be used if they do not appear uniformly white and cloudy after re-suspension.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Monotard 100 IU/ml
Suspension for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin human, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).

1 ml contains 100 IU of insulin human
1 vial contains 10 ml equivalent to 1000 IU

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Monotard is an insulin zinc suspension. The suspension consists of a mixture of amorphous and crystalline particles (ratio 3:7).

For excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for injection in a vial.

Monotard is a cloudy, white, aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

Monotard is a long-acting insulin.

Dosage
Dosage is individual and determined by the physician in accordance with the needs of the patient. The average range of total daily insulin requirement for maintenance therapy in type 1 diabetic patients lies between 0.5 and 1.0 IU/kg. In pre-pubertal children it usually varies from 0.7 to 1.0 IU/kg. During the period of partial remission, the insulin requirements can be much lower, whereas in insulin resistant states e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher.

Initial dosages for type 2 diabetic patients are often lower, e.g. 0.3 to 0.6 IU/kg/day.

The physician determines whether one or several daily injections are necessary. Monotard may be used alone or mixed with fast-acting insulin. In intensive insulin therapy the suspension may be used as basal insulin (evening and/or morning injection) with fast-acting insulin given at meals.

In patients with diabetes mellitus optimised glycaemic control delays the onset and slows the progression of late diabetic complications. Blood glucose monitoring is therefore recommended.

Dosage adjustment
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.

Renal or hepatic impairment may reduce insulin requirement.

Adjustment of dosage may also be necessary if patients change physical activity or their usual diet. Dosage adjustment may be necessary when transferring patients from one insulin preparation to another (see section 4.4 Special warnings and special precautions for use).

Administration
For subcutaneous use.

Monotard is usually administered subcutaneously in the thigh. If convenient, the abdominal wall, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites.

Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.
Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.
Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Insulin suspensions are never to be administered intravenously.

Monotard is accompanied by a package leaflet with detailed instruction for use to be followed.

The vials are for use with insulin syringes with a corresponding unit scale.

4.3 Contraindications

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Hypersensitivity to human insulin or to any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and special precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to **hyperglycaemia** and diabetic ketoacidosis.
Usually the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath (see section 4.8 Undesirable effects).
In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.
Hypoglycaemia can generally be corrected by immediate carbohydrate intake. In order to be able to take action immediately, patients should carry glucose with them at all times.
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly (see section 4.8 Undesirable effects).
Usual warning symptoms may disappear in patients with longstanding diabetes.
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If an adjustment is needed when switching the patients to Monotard, it may occur with the first dose or during the first several weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or

different from those experienced with their previous insulin.

Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.

Insulin suspensions are not to be used in insulin infusion pumps.

Monotard contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

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A number of medicinal products are known to interact with the glucose metabolism. The physician must therefore take possible interactions into account and should always ask their patients about any medicinal products they take.

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Oral hypoglycaemic agents (OHA), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates and alcohol.

The following substances may increase insulin requirement:
Thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide/ laneotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.
Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.
After delivery, insulin requirements return rapidly to pre-pregnancy values.

Insulin treatment of the nursing mother presents no risk to the baby. However, the Monotard dosage may need to be adjusted.

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. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
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 signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

The most often seen undesirable effect in insulin-treated patients is a change in blood glucose levels. **From clinical investigations it is known that major hypoglycaemia, defined as need for assistance in treatment, occurs in approximately 20% of well-controlled patients.** Based on post-marketing experience adverse drug reactions including hypoglycaemia have been reported rarely (>1/10,000 <1/1,000). The listings below are all based on post-marketing experience and is subject to underreporting and should be interpreted in that light.

Metabolism and nutrition disorders

Rare (>1/10,000 <1/1,000)	
Change in blood glucose	Hypoglycaemia: Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. Hyperglycaemia: Usually the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis which is potentially lethal. For precautions see section 4.4 Special warnings and special precautions for use.

Eye disorders

Very rare (<1/10,000)	Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

General disorders and administration site conditions

Very rare (<1/10,000)	Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.
Very rare (<1/10,000)	Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.
Very rare (<1/10,000)	Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Very rare (<1/10,000)	Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

4.9 Overdose

A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.
  Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiabetic agent. ATC code: A10A C01.

The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Monotard is a long-acting insulin.
Onset of action is within 2½ hours, reaches a maximum effect within 4-15 hours and the entire time of duration is approximately 24 hours.

5.2 Pharmacokinetic properties

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulins is therefore affected by significant intra- and inter-individual variation.

Absorption
The maximum plasma concentration of the insulins is reached within 2-18 hours after subcutaneous administration.

Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism
Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin

molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination
The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{½}$) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ of about 9-15 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride
Zinc acetate
Sodium chloride
Methyl parahydroxybenzoate
Sodium acetate
Sodium hydroxide or/and hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Insulin suspensions should not be added to infusion fluids.
Medicinal products added to the insulin suspension may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.
Mixing of Monotard with phosphate buffered insulin preparations is not recommended due to the risk of precipitation of zinc-phosphate, leading to an unpredictable timing of such insulin mixtures. When mixing Actrapid with Monotard immediate injection is necessary to avoid blunting of the fast acting effect of Actrapid.

6.3 Shelf life

30 months.

After first opening: 6 weeks.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator) not near a freezing compartment.
Do not freeze.
Keep the container in the outer carton in order to protect from light.

During use: do not refrigerate. Do not store above 25°C.

Protect from excessive heat and sunlight.

6.5 Nature and contents of container

Glass vial (type 1) closed with a bromobutyl/polyisoprene rubber stopper and a protective tamperproof plastic cap.
Pack sizes: 1 and 5 vials x 10 ml.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Insulin preparations, which have been frozen, must not be used.
Insulin suspensions should not be used if they do not appear uniformly white and cloudy after re-suspension.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsvaerd
Denmark

Name and address of the manufacturers responsible for batch release

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsvaerd
Denmark

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Monotard 40 IU/ml
Suspension for injection in a vial
Insulin human, rDNA

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml suspension contains 40 IU (1.4 mg) of insulin human, rDNA

3. LIST OF EXCIPIENTS

zinc chloride, zinc acetate, sodium chloride, methyl parahydroxybenzoate, sodium acetate, sodium hydroxide, hydrochloric acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Resuspend according to instructions
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)
Do not freeze
Keep the container in the outer carton
During use: do not refrigerate or store above 25°C

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

Novo Nordisk A/S
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Monotard 40 IU/ml
Suspension for injection in a vial
Insulin human, rDNA

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml suspension contains 40 IU (1.4 mg) of insulin human, rDNA

3. LIST OF EXCIPIENTS

zinc chloride, zinc acetate, sodium chloride, methyl parahydroxybenzoate, sodium acetate, sodium hydroxide, hydrochloric acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Resuspend according to instructions
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)
Do not freeze
Keep the container in the outer carton
During use: do not refrigerate or store above 25°C

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

Novo Nordisk A/S
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Monotard 40 IU/ml
Suspension for injection
Insulin human, rDNA

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Monotard 100 IU/ml
Suspension for injection in a vial
Insulin human, rDNA

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml suspension contains 100 IU (3.5 mg) of insulin human, rDNA

3. LIST OF EXCIPIENTS

zinc chloride, zinc acetate, sodium chloride, methyl parahydroxybenzoate, sodium acetate, sodium hydroxide, hydrochloric acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Resuspend according to instructions
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)
Do not freeze
Keep the container in the outer carton
During use: do not refrigerate or store above 25°C

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

Novo Nordisk A/S
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Monotard 100 IU/ml
Suspension for injection in a vial
Insulin human, rDNA

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml suspension contains 100 IU (3.5 mg) of insulin human, rDNA

3. LIST OF EXCIPIENTS

zinc chloride, zinc acetate, sodium chloride, methyl parahydroxybenzoate, sodium acetate, sodium hydroxide, hydrochloric acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Resuspend according to instructions
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)
Do not freeze
Keep the container in the outer carton
During use: do not refrigerate or store above 25°C

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

Novo Nordisk A/S
DK-2880 Bagsværd
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12. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Monotard 100 IU/ml
Suspension for injection
Insulin human, rDNA

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

Expiry

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

B. PACKAGE LEAFLET

Monotard

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor, diabetes nurse or pharmacist. This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Monotard 40 IU/ml Suspension for injection in a vial
Suspension for injection in a vial. Insulin human, rDNA.
Monotard is a zinc suspension consisting of a mixture of amorphous and crystalline particles (ratio 3:7).
The active substance is insulin human made by recombinant biotechnology.
1 ml contains 40 IU of insulin human. 1 vial contains 10 ml equivalent to 400 IU.
Monotard also contains zinc chloride, zinc acetate, sodium chloride, methyl parahydroxy benzoate, sodium actetate, sodium hydroxide, hydrochloric acid and water for injections.
The suspension for injection comes as a white, cloudy aqueous suspension in packs of 1 or 5 vials of 10 ml (not all packs may be marketed).
The marketing authorisation holder and manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

1 What Monotard is

Monotard is human insulin to treat diabetes. It comes in a 10 ml vial that you use to fill a syringe. Monotard is a long-acting insulin. This means that it will start to lower your blood sugar about 2 ½ hours after you take it, and the effect will last for approximately 24 hours. Monotard is often given in combination with fast-acting insulins.

2 Before you use Monotard

Do not use Monotard
- ► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See 4 What to do in an emergency for more about hypos
- ► If you have ever had an allergic reaction to this insulin product or any of the ingredients (see box, below left). Some people are allergic to the ingredient methyl parahydroxy benzoate. Look out for the signs of allergy in 5 Possible side effects.

Take special care with Monotard
- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
- ► If you are drinking alcohol: watch for signs of a hypo
- ► If you are exercising more than usual or if you want to change your usual diet
- ► If you are ill: carry on taking your insulin
- ► If you are going abroad: travelling over time zones may affect your insulin needs
- ► If you are pregnant, or planning a pregnancy: you must be especially careful to control your blood sugar; too much or too little could harm your health and the baby's
- ► If you are breastfeeding: there's no risk to the baby, but you may need to adjust your insulin and your diet
- ► If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

Other medicines and Monotard
Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most important medicines which may affect your insulin treatment. Talk to your

doctor if you take or change any other medicines, even those not-prescribed.
Your need for insulin may change if you also take: oral hypoglycaemic agents; monoamine oxidase inhibitors (MAOI); certain beta-blockers; ACE-inhibitors; acetylsalicylic acid; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

3 Using Monotard

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully**.** This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Before using Monotard
- ► Make sure it is the right type of insulin
- ► Disinfect the rubber membrane with surgical spirit.

Do not use Monotard
- ► If the protective cap is loose or missing. Each vial has a protective, tamperproof plastic cap. If it isn't in perfect condition when you get the vial, return the vial to your supplier
- ► If it hasn't been stored correctly or been frozen (see 6 How to store Monotard)
- ► If it's not uniformly white and cloudy when it's mixed.

How to use this insulin
Monotard is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle. Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). The best place to give yourself an injection is the front of your thighs. If convenient, the front of your waist (abdomen), your buttocks or the front of your upper arms may be used.
You should always measure your blood glucose regularly.
Monotard vials are for use with insulin syringes with the corresponding unit scale.

To inject Monotard on its own
- Before first use and just before injecting this insulin, shake the vial up and down at least 10 times and roll the vial between your hands. Repeat this procedure if necessary until the liquid is uniformly white and cloudy
- Draw air into the syringe, in the same amount as the dose of insulin you need
- Inject the air into the vial: push the needle through the rubber stopper and press the plunger
- Turn the vial and syringe upside down
- Draw the right dose of insulin into the syringe
- Pull the needle out of the vial
- Make sure there is no air left in the syringe: point the needle upwards and push the air out
- Check you have the right dose
- Inject straight away.

To mix Monotard with fast acting insulin
- Before first use and just before injecting Monotard, shake the vial up and down at least 10 times and roll the vial between your hands. Repeat this procedure if necessary until the liquid is uniformly white and cloudy
- Draw as much air into the syringe as the dose of Monotard you need. Inject the air into the Monotard vial, then pull out the needle
- Draw as much air into the syringe as the dose of fast acting insulin you need. Inject the air into the fast acting insulin vial. Then turn the vial and syringe upside down
- Draw the right dose of fast acting insulin into the syringe. Pull the needle out of the vial. Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose

- Now push the needle into the vial of Monotard. Then turn the vial and syringe upside down
- Draw the right dose of Monotard into the syringe. Pull the needle out of the vial. Make sure there's no air left in the syringe, and check the dose
- Inject the mixture straight away.

Always mix fast acting and long acting insulin in this order.

Inject the insulin
- Inject the insulin under the skin. Use the injection technique advised by your doctor or diabetes nurse
- Keep the needle under your skin for at least 6 seconds to make sure the full dose has been delivered.

4 What to do in an emergency

If you get a hypo
A hypo means your blood sugar level is too low.
The **warning signs of a hypo** may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell people that **if you pass out** (become unconscious), they should: turn you on your side and get medical help straight away. They should not give you any food or drink. It could choke you.
► If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death
► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo
You get a hypo if your blood sugar gets too low. This might happen:
- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high
Your blood sugar may get too high (this is called hyperglycaemia).
The **warning signs** appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity smell of the breath.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of a hyperglycaemia
- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5 Possible side effects

Like all medicines, Monotard can have side effects.

Common side effects (up to 10%)

Low or high blood sugar (hypo or hyperglycaemia). Taking too much or too little Monotard may cause respectively hypo or hyperglycaemia. See the advice in 4 What to do in an emergency.

Rare side effects (up to 0.1%)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes at the injection site. Reactions (redness, swelling, itching) at the injection site may occur and will normally disappear during use. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same area.

Signs of allergy. Very rarely, people get redness, swelling or itching around the area of the insulin injection (local allergic reactions). These usually go away after a few weeks of taking your insulin. If they do not go away, see your doctor.
Seek medical advice straight away:
- ► If signs of allergy spread to other parts of your body, or
- ► If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Monotard or one of its ingredients (called a systemic allergic reaction). See also the warning in 2 Before you use Monotard.

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon goes away.

If you notice any side effects, also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6 How to store Monotard

Keep out of the reach and sight of children.
Monotard vials that are **not being used** are to be stored in the fridge at 2°C - 8°C, away from the freezer compartment. Do not freeze.
Monotard vials that are **being used** or about to be used are not to be kept in the fridge. You can carry them with you and keep them at room temperature (below 25°C) for up to 6 weeks.
Always keep the vial in the outer carton when you're not using it in order to protect it from light.
Monotard should be protected from excessive heat and sunlight.
Do not use Monotard after the expiry date stated on the label and the carton.

Leaflet last approved on

Monotard

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor, diabetes nurse or pharmacist. This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Monotard 100 IU/ml Suspension for injection in a vial
Suspension for injection in a vial. Insulin human, rDNA.
Monotard is a zinc suspension consisting of a mixture of amorphous and crystalline particles (ratio 3:7).
The active substance is insulin human made by recombinant biotechnology.
1 ml contains 100 IU of insulin human. 1 vial contains 10 ml equivalent to 1000 IU.
Monotard also contains zinc chloride, zinc acetate, sodium chloride, methyl parahydroxy benzoate, sodium acetate, sodium hydroxide, hydrochloric acid and water for injections.
The suspension for injection comes as a white, cloudy aqueous suspension in packs of 1 or 5 vials of 10 ml (not all packs may be marketed).
The marketing authorisation holder and manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

1 What Monotard is

Monotard is human insulin to treat diabetes. It comes in a 10 ml vial that you use to fill a syringe. Monotard is a long-acting insulin. This means that it will start to lower your blood sugar about 2 ½ hours after you take it, and the effect will last for approximately 24 hours. Monotard is often given in combination with fast-acting insulins.

2 Before you use Monotard

Do not use Monotard
- ► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is symptoms of low blood sugar). See 4 What to do in an emergency for more about hypos
- ► If you have ever had an allergic reaction to this insulin product or any of the ingredients (see box, below left). Some people are allergic to the ingredient methyl parahydroxy benzoate. Look out for the signs of allergy in 5 Possible side effects.

Take special care with Monotard
- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
- ► If you are drinking alcohol: watch for signs of a hypo
- ► If you are exercising more than usual or if you want to change your usual diet
- ► If you are ill: carry on taking your insulin
- ► If you are going abroad: travelling over time zones may affect your insulin needs
- ► If you are pregnant, or planning a pregnancy: you must be especially careful to control your blood sugar; too much or too little could harm your health and the baby's
- ► If you are breastfeeding: there's no risk to the baby, but you may need to adjust your insulin and your diet
- ► If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

Other medicines and Monotard
Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most important medicines which may affect your insulin treatment. Talk to your

doctor if you take or change any other medicines, even those not-prescribed.
Your need for insulin may change if you also take: oral hypoglycaemic agents; monoamine oxidase inhibitors (MAOI); certain beta-blockers; ACE-inhibitors; acetylsalicylic acid; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

3 Using Monotard

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully**.** This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Before using Monotard
- ► Make sure it is the right type of insulin
- ► Disinfect the rubber membrane with surgical spirit.

Do not use Monotard
- ► If the protective cap is loose or missing. Each vial has a protective, tamperproof plastic cap. If it isn't in perfect condition when you get the vial, return the vial to your supplier
- ► If it hasn't been stored correctly or been frozen (see 6 How to store Monotard)
- ► If it's not uniformly white and cloudy when it's mixed.

How to use this insulin
Monotard is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle. Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). The best place to give yourself an injection is the front of your thighs. If convenient, the front of your waist (abdomen), your buttocks or the front of your upper arms may be used.
You should always measure your blood glucose regularly.
Monotard vials are for use with insulin syringes with the corresponding unit scale.

To inject Monotard on its own
- Before first use and just before injecting this insulin, shake the vial up and down at least 10 times and roll the vial between your hands. Repeat this procedure if necessary until the liquid is uniformly white and cloudy
- Draw air into the syringe, in the same amount as the dose of insulin you need
- Inject the air into the vial: push the needle through the rubber stopper and press the plunger
- Turn the vial and syringe upside down
- Draw the right dose of insulin into the syringe
- Pull the needle out of the vial
- Make sure there is no air left in the syringe: point the needle upwards and push the air out
- Check you have the right dose
- Inject straight away.

To mix Monotard with fast acting insulin
- Before first use and just before injecting Monotard, shake the vial up and down at least 10 times and roll the vial between your hands. Repeat this procedure if necessary until the liquid is uniformly white and cloudy
- Draw as much air into the syringe as the dose of Monotard you need. Inject the air into the Monotard vial, then pull out the needle
- Draw as much air into the syringe as the dose of fast acting insulin you need. Inject the air into the fast acting insulin vial. Then turn the vial and syringe upside down
- Draw the right dose of fast acting insulin into the syringe. Pull the needle out of the vial.
- Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose

- Now push the needle into the vial of Monotard. Then turn the vial and syringe upside down
- Draw the right dose of Monotard into the syringe. Pull the needle out of the vial. Make sure there's no air left in the syringe, and check the dose
- Inject the mixture straight away.

Always mix fast acting and long acting insulin in this order.

Inject the insulin
- Inject the insulin under the skin. Use the injection technique advised by your doctor or diabetes nurse
- Keep the needle under your skin for at least 6 seconds to make sure the full dose has been delivered.

4 What to do in an emergency

If you get a hypo
A hypo means your blood sugar level is too low.
The **warning signs of a hypo** may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.
If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.
Don't take any insulin if you feel a hypo coming on.
Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.
Tell people that **if you pass out** (become unconscious), they should: turn you on your side and get medical help straight away. They should not give you any food or drink. It could choke you.
- ► If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death
- ► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

Causes of a hypo
You get a hypo if your blood sugar gets too low. This might happen:
- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high
Your blood sugar may get too high (this is called hyperglycaemia).
The **warning signs** appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity smell of the breath.
If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice straight away.
These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of a hyperglycaemia
- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

5 Possible side effects

Like all medicines, Monotard can have side effects.

Common side effects (up to 10%)

Low or high blood sugar (hypo or hyperglycaemia). Taking too much or too little Monotard may cause respectively hypo or hyperglycaemia. See the advice in 4 What to do in an emergency.

Rare side effects (up to 0.1%)

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes at the injection site. Reactions (redness, swelling, itching) at the injection site may occur and will normally disappear during use. If you inject yourself too often in the same site, lumps may develop underneath. Prevent this by choosing different injection sites each time within the same area.

Signs of allergy. Very rarely, people get redness, swelling or itching around the area of the insulin injection (local allergic reactions). These usually go away after a few weeks of taking your insulin. If they do not go away, see your doctor.
Seek medical advice straight away:
- ► If signs of allergy spread to other parts of your body, or
- ► If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Monotard or one of its ingredients (called a systemic allergic reaction). See also the warning in 2 Before you use Monotard.

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon goes away.

If you notice any side effects, also those not mentioned in this leaflet, please inform your doctor or pharmacist.

6 How to store Monotard

Keep out of the reach and sight of children.
Monotard vials that are **not being used** are to be stored in the fridge at 2°C - 8°C, away from the freezer compartment. Do not freeze.
Monotard vials that are **being used** or about to be used are not to be kept in the fridge. You can carry them with you and keep them at room temperature (below 25°C) for up to 6 weeks.
Always keep the vial in the outer carton when you're not using it in order to protect it from light.
Monotard should be protected from excessive heat and sunlight.
Do not use Monotard after the expiry date stated on the label and the carton.

Leaflet last approved on