ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Actrapid 100 international units/ml solution for injection in vial.
Actrapid Penfill 100 international units/ml solution for injection in cartridge.
Actrapid FlexPen 100 international units/ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Actrapid vial (100 international units/ml)
1 vial contains 10 ml equivalent to 1,000 international units. 1 ml solution contains 100 international units insulin human* (equivalent to 3.5 mg).

Actrapid Penfill
1 cartridge contains 3 ml equivalent to 300 international units. 1 ml solution contains 100 international units insulin human* (equivalent to 3.5 mg).

Actrapid FlexPen
1 pre-filled pen contains 3 ml equivalent to 300 international units. 1 ml solution contains 100 international units insulin human* (equivalent to 3.5 mg).

*Human insulin is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

Excipient with known effect:

Actrapid contains less than 1 mmol sodium (23 mg) per dose, i.e. Actrapid is essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Actrapid is indicated for treatment of diabetes mellitus.

4.2 Posology and method of administration

Posology

The potency of human insulin is expressed in international units.

Actrapid dosing is individual and determined in accordance with the needs of the patient. It can be used alone or in combination with intermediate-acting or long-acting insulin before a meal or a snack.

The individual insulin requirement is usually between 0.3 and 1.0 international unit/kg/day.
Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly (≥ 65 years old)
Actrapid can be used in elderly patients.
In elderly patients, glucose monitoring should be intensified and the insulin dose adjusted on an individual basis.

Renal and hepatic impairment
Renal or hepatic impairment may reduce the patient's insulin requirements.
In patients with renal or hepatic impairment, glucose monitoring should be intensified and the human insulin dose adjusted on an individual basis.

Paediatric population
Actrapid can be used in children and adolescents.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the Actrapid dose and the dose of the basal insulin may be necessary.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

Actrapid is a fast-acting human insulin and may be used in combination with intermediate or long-acting insulin medicinal products.

Actrapid is administered subcutaneously by injection in the abdominal wall, the thigh, the gluteal region or the deltoid region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8). Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.

The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected. Subcutaneous injection into the abdominal wall ensures a faster absorption than other injection sites. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

Due to the risk of precipitation in pump catheters, Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

Actrapid vial (100 international units/ml)
Intravenous use

If necessary, Actrapid can be administered intravenously. This should be carried out by healthcare professionals.

For intravenous use, infusion systems with Actrapid at concentrations from 0.05 international unit/ml to 1.0 international unit/ml human insulin in the infusion fluids 0.9% sodium chloride, 5% dextrose and 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours. Although stable over time, a certain amount of insulin will initially be adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the insulin infusion.

For detailed user instructions, please refer to the package leaflet.

Actrapid vial (100 international units/ml)
Administration with a syringe
Actrapid vials are for use with insulin syringes with a corresponding unit scale. When two types of insulin are mixed always mix the insulin medicinal products in the same sequence.

Actrapid Penfill
Administration with an insulin delivery system
Actrapid Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. Actrapid Penfill is only suitable for subcutaneous injections from a reusable pen. If administration by syringe or intravenous injection is necessary, a vial should be used.

Actrapid FlexPen
Administration with FlexPen
Actrapid FlexPen is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. FlexPen delivers 1-60 units in increments of 1 unit. Actrapid FlexPen is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used.

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

Before travelling between different time zones, the patient should seek the doctor's advice since this may mean that the patient has to take the insulin and meals at different times.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycaemia develop 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.

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, Actrapid must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.8 and 4.9).

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. Usual warning symptoms may disappear in patients with longstanding diabetes.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal insulin, human insulin or insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dose. Patients transferred to Actrapid from another type of insulin may require an increased number of daily injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Actrapid.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Combination of Actrapid 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 Actrapid 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.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Actrapid and other insulin products.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirement:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the patient's insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 blood glucose control and monitoring of pregnant women with diabetes are 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 normally return rapidly to pre-pregnancy values.

Breast-feeding

There is no restriction on treatment with Actrapid during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the Actrapid dose may need to be adjusted.

Fertility

Animal reproduction studies with human insulin have not revealed any adverse effects on fertility.

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 while 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

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of a transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: 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).

Immune system disorders	Uncommon – Urticaria, rash
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Uncommon – Peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – Refraction disorders
	Very rare – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Injection site reactions
	Uncommon – Oedema

* see Description of selected adverse reactions
† ADR from postmarketing sources.

Description of selected adverse reactions

Anaphylactic reactions
The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulty in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The 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 concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control.

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis 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 (see section 4.4).

Paediatric population

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A specific overdose of insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high a dose relative to the patient's requirement is administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.
  Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, fast-acting, insulin (human). ATC code: A10AB01.

Mechanism of action and pharmacodynamic effects

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.

A clinical trial in a single intensive care unit treating hyperglycaemia (blood glucose above 10 mmol/l) in 204 diabetic and 1344 non-diabetic patients undergoing major surgery showed that normoglycaemia (blood glucose 4.4 – 6.1 mmol/l) induced by intravenous Actrapid reduced mortality by 42% (8% versus 4.6%).

Actrapid is a fast-acting insulin.
Onset of action is within ½ hour, reaches a maximum effect within 1.5–3.5 hours and the entire duration of action is approximately 7–8 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 dose, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin medicinal products are therefore affected by significant intra- and inter-individual variation.

Absorption

The maximum plasma concentration is reached within 1.5–2.5 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 2-5 hours.

Paediatric population

The pharmacokinetic profile of Actrapid has been studied in a small number (n=18) of diabetic children (aged 6–12 years) and adolescents (aged 13–17 years). The data are limited but suggest that the pharmacokinetic profile in children and adolescents may be similar to that in adults. However, there were differences between age groups in $C_{max,}$ stressing the importance of individual dose titration.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride
Glycerol
Metacresol
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Insulin medicinal products should only be added to compounds with which it is known to be compatible. Medicinal products added to the insulin solution may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulfites.

6.3 Shelf life

Before opening: 30 months when stored in a refrigerator (2°C – 8°C).

If there are 6 months or more until the expiry date, the product may be stored outside of the refrigerator (below 30˚C) for a maximum of 4 weeks before it is taken into use or carried as a spare. Keep the product in the outer carton in order to protect from light. After storage outside of the refrigerator, the product must not be returned to the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

Actrapid vial (100 international units/ml)
During use or when carried as a spare: The product can be stored for a maximum of 6 weeks. Store below 30°C. Please record the beginning of use on the product carton.

Actrapid Penfill/Actrapid FlexPen
During use or when carried as a spare: The product can be stored for a maximum of 6 weeks. Store below 30°C.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C – 8°C). Do not freeze. For optional storage below 30˚C, see section 6.3.

Actrapid vial (100 international units/ml)
During use or when carried as a spare: Store below 30°C. Do not refrigerate or freeze.
Keep the vial in the outer carton in order to protect from light.

Actrapid Penfill
During use or when carried as a spare: Store below 30°C. Do not refrigerate or freeze.
Keep the cartridge in the outer carton in order to protect from light.

Actrapid FlexPen
During use or when carried as a spare: Store below 30°C. Do not refrigerate or freeze.
Keep the pen cap on the pen in order to protect from light.

6.5 Nature and contents of container

Actrapid vial (100 international units/ml)
Vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of solution.

Pack sizes of 1 and 5 vials of 10 ml. Not all pack sizes may be marketed.

Actrapid Penfill
Cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of solution.

Pack sizes of 1, 5 and 10 cartridges. Not all pack sizes may be marketed.

Actrapid FlexPen
Cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of solution in a pre-filled multidose disposable pen made of polypropylene.

Pack sizes of 1, 5 and 10 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

Actrapid which has been frozen must not be used.

The patient should be advised to discard the needle and syringe after each injection.

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

Needles, syringes, cartridges and pre-filled-pens must not be shared.

The cartridge must not be refilled.

7. SCIENTIFIC OPINION HOLDER

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

8. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE SCIENTIFIC OPINION

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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

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

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Name and address of the manufacturers responsible for batch release

Actrapid vial, Penfill and FlexPen:

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

Novo Nordisk Production SAS
45, Avenue d'Orléans
F-28000 Chartres
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 scientific opinion holder 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

Actrapid 100 IU/ml
Solution for injection
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial contains 10 ml equivalent to 1,000 IU. 1 ml solution contains 100 IU insulin human (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide/hydrochloric acid for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTES 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, IF NECESSARY

Use only clear and colourless solutions

8. EXPIRY DATE

EXP/
During use or when carried as a spare: Use within 6 weeks. Taken in use:_____

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator. Do not freeze. May be stored below 30°C for up to 4 weeks before use, if there are 6 months or more until EXP. Taken out of refrigerator:_____
During use: Store below 30°C. Do not refrigerate or 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

Discard the needle and syringe after each injection

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

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

12. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (VIAL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Actrapid 100 IU/ml
Solution for injection
insulin human
SC, IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

Actrapid Penfill 100 IU/ml
Solution for injection in cartridge
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE

1 cartridge contains 3 ml equivalent to 300 IU. 1 ml solution contains 100 IU insulin human (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide/hydrochloric acid for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 3 ml cartridge
5 x 3 ml cartridges
10 x 3 ml cartridges

5. METHOD AND ROUTE 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 WARNINGS, IF NECESSARY

Use only clear and colourless solutions
For use by one person only

8. EXPIRY DATE

EXP/
During use or when carried as a spare: Use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator. Do not freeze. May be stored below 30°C for up to 4 weeks before use, if there are 6 months or more until EXP. Taken out of refrigerator:_____
During use: Store below 30°C. Do not refrigerate or 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

Discard the needle after each injection

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

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

12. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid Penfill

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Actrapid Penfill 100 IU/ml
Solution for injection
insulin human
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT

Actrapid FlexPen 100 IU/ml
Solution for injection in pre-filled pen
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen contains 3 ml equivalent to 300 IU. 1 ml solution contains 100 IU insulin human (equivalent to 3.5 mg),

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide/hydrochloric acid for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
10 x 3 ml pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use
Needles are not included

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 WARNINGS, IF NECESSARY

Use only clear and colourless solutions
For use by one person only
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP/
During use or when carried as a spare: Use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator. Do not freeze. May be stored below 30°C for up to 4 weeks before use, if there are 6 months or more until EXP. Taken out of refrigerator:_____
During use: Store below 30°C. Do not refrigerate or freeze
Keep the pen cap on 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

Discard the needle after each injection

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

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

12. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid FlexPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Actrapid FlexPen 100 IU/ml
Solution for injection
insulin human
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Actrapid 100 IU/ml (international units/ml) solution for injection in vial
human insulin

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. See section 4.

1. What Actrapid is and what it is used for

Actrapid is human insulin with a fast-acting effect.

Actrapid is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Treatment with Actrapid helps to prevent complications from your diabetes.

Actrapid will start to lower your blood sugar about half an hour after you inject it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with intermediate-acting or long-acting insulin preparations.

2. What you need to know before you use Actrapid

Do not use Actrapid

- ► If you are allergic to human insulin or any of the other ingredients in this medicine, see section 6.
- ► If you suspect hypoglycaemia (low blood sugar) is starting, see Summary of serious and very common side effects in section 4.
- ► In insulin infusion pumps.
- ► If the protective cap is loose or missing. Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- ► If it has not been stored correctly or if it has been frozen, see section 5.
- ► If the insulin does not appear clear and colourless.

If any of these apply, do not use Actrapid. Talk to your doctor, pharmacist or nurse for advice.

Before using Actrapid

- ► Check the label to make sure it is the right type of insulin.
- ► Remove the protective cap.
- ► Always use a new needle for each injection to prevent contamination.
- ► Needles and syringes must not be shared.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:
- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ► If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.

► If you are ill, carry on taking your insulin and consult your doctor.
► If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and Actrapid

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines affect your blood sugar level, and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormone (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes 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).

If you have taken any of the medicines listed here, tell your doctor, pharmacist or nurse.

Actrapid with alcohol

► If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

► If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Actrapid can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
► There are no restrictions on treatment with Actrapid during breast-feeding.

Ask your doctor, pharmacist or nurse for advice before taking this medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Actrapid contains sodium

Actrapid contains less than 1 mmol sodium (23 mg) per dose, i.e. Actrapid is essentially 'sodium-free'.

3. How to use Actrapid

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection to avoid low blood sugar.

Do not change your insulin unless your doctor tells you to. 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.

Use in children and adolescents

Actrapid can be used in children and adolescents.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

Actrapid is administered by injection under the skin (subcutaneously). You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary Actrapid can be given directly into a vein, but this must only be done by healthcare professionals.

With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting, see section 4. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to take Actrapid

Actrapid vials are for use with insulin syringes with the corresponding unit scale.

If you only use one type of insulin
1. Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.
2. Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.

If you have to mix two types of insulin
1. Just before use, roll the vial of intermediate- or long-acting (cloudy) insulin between your hands until the liquid is uniformly white and cloudy.
2. Draw into the syringe the same amount of air as the dose of intermediate- or long-acting insulin. Inject the air into the vial containing intermediate- or long-acting insulin and pull out the needle.
3. Draw into the syringe the same amount of air as the dose of Actrapid. Inject the air into the vial containing Actrapid. Then turn the vial and syringe upside down and draw up the prescribed dose of Actrapid. Expel any air from the syringe and check that the dose is correct.
4. Push the needle into the vial of intermediate- or long-acting insulin, turn the vial and syringe upside down and draw out the dose you have been prescribed. Expel any air from the syringe and check that the dose is correct. Inject the mixture immediately.
5. Always mix Actrapid and intermediate- or long-acting insulin in the same sequence.

How to inject Actrapid

- ► Inject the insulin under your skin. Use the injection technique advised by your doctor or nurse.
- ► Keep the needle under your skin for at least 6 seconds to make sure that you have injected all the insulin.
- ► Discard the needle and syringe after each injection.

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low (hypoglycaemia). See Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin your blood sugar may get too high (hyperglycaemia). See Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol, see Actrapid with alcohol in section 2.

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. 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 sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
- ► If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ► When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink, because you may choke.

Serious allergic reaction to Actrapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

List of other side effects

Uncommon side effects
May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Very rare side effects
May affect less than 1 in 10,000 people.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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 (acetone) smell of the breath.

What to do if you experience high blood sugar:
- ► If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ► These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store Actrapid

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 vial label and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening: Store in a refrigerator at 2°C – 8°C. Keep away from the cooling element. Do not freeze. If there are 6 months or more until the expiry date, the product may be stored outside of the refrigerator (below 30°C) for up to 4 weeks before it is taken into use or carried as a spare. Always keep the vial in the outer carton when you are not using it, in order to protect from light. The product must not be returned to the refrigerator after it has been stored outside of the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

During use or when carried as a spare: Do not refrigerate or freeze. You can carry it with you and keep it at room temperature (below 30ºC) for up to 6 weeks. Please record the beginning of use on the product carton.

Always keep the vial in the outer carton when you are not using it, in order to protect from light.

Discard the needle and syringe after each injection.

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 Actrapid contains

- The active substance is human insulin. Each ml contains 100 IU of human insulin. Each vial contains 1,000 IU of human insulin in 10 ml solution for injection.
- The other ingredients are zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

What Actrapid looks like and contents of the pack

Actrapid is presented as a solution for injection.
Pack sizes of 1 or 5 vials of 10 ml. Not all pack sizes may be marketed.

The solution is clear and colourless.

Scientific Opinion Holder

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

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are S6 or ZF, the manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

- If the second and third characters are T6, the manufacturer is Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France.

This leaflet was last revised in

Other sources of information

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

Package leaflet: Information for the user

Actrapid Penfill 100 IU/ml (international units/ml) solution for injection in cartridge
human insulin

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. See section 4.

What is in this leaflet

1. What Actrapid is and what it is used for

Actrapid is human insulin with a fast-acting effect.

Actrapid is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Treatment with Actrapid helps to prevent complications from your diabetes.

Actrapid will start to lower your blood sugar about half an hour after you inject it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with intermediate-acting or long-acting insulin preparations.

2. What you need to know before you use Actrapid

Do not use Actrapid

- ► If you are allergic to human insulin or any of the other ingredients in this medicine, see section 6.
- ► If you suspect hypoglycaemia (low blood sugar) is starting, see Summary of serious and very common side effects in section 4.
- ► In insulin infusion pumps.
- ► If the cartridge or the device containing the cartridge is dropped, damaged or crushed.
- ► If it has not been stored correctly or if it has been frozen, see section 5.
- ► If the insulin does not appear clear and colourless.

If any of these apply, do not use Actrapid. Talk to your doctor, pharmacist or nurse for advice.

Before using Actrapid

- ► Check the label to make sure it is the right type of insulin.
- ► Always check the cartridge, including the rubber plunger at the bottom of the cartridge. Do not use it if any damage is seen or if the rubber plunger has been drawn above the white label band

at the bottom of the cartridge. This could be the result of an insulin leakage. If you suspect that the cartridge is damaged, take it back to your supplier. See your pen manual for further instructions.
- ► Always use a new needle for each injection to prevent contamination.
- ► Needles and Actrapid Penfill must not be shared.
- ► Actrapid Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:
- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ► If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- ► If you are ill, carry on taking your insulin and consult your doctor.
- ► If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and Actrapid

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines affect your blood sugar level, and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormone (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes 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).

If you have taken any of the medicines listed here, tell your doctor, pharmacist or nurse.

Actrapid with alcohol

► If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

► If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Actrapid can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
► There are no restrictions on treatment with Actrapid during breast-feeding.

Ask your doctor, pharmacist or nurse for advice before taking this medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Actrapid contains sodium

Actrapid contains less than 1 mmol sodium (23 mg) per dose, i.e. Actrapid is essentially 'sodium-free'.

3. How to use Actrapid

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection to avoid low blood sugar.

Do not change your insulin unless your doctor tells you to. 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.

Use in children and adolescents

Actrapid can be used in children and adolescents.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

Actrapid is administered by injection under the skin (subcutaneously). You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). Actrapid Penfill is only suitable for injecting under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting, see section 4. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

- ► Do not refill the cartridge. Once empty, it must be disposed of.
- ► Actrapid Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles.
- ► If you are treated with Actrapid Penfill and another insulin Penfill cartridge, you should use two insulin delivery systems, one for each type of insulin.
- ► Always carry a spare Penfill cartridge in case the one in use is lost or damaged.

How to inject Actrapid

- ► Inject the insulin under your skin. Use the injection technique advised by your doctor or nurse and as described in your pen manual.
- ► Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- ► After each injection, be sure to remove and discard the needle and store Actrapid without the needle attached. Otherwise the liquid may leak out, which can cause inaccurate dosing.

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low (hypoglycaemia). See Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin your blood sugar may get too high (hyperglycaemia). See Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol, see Actrapid with alcohol in section 2.

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. 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 sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
- ► If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ► When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink, because you may choke.

Serious allergic reaction to Actrapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often

this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

List of other side effects

Uncommon side effects
May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Very rare side effects
May affect less than 1 in 10,000 people.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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 (acetone) smell of the breath.

What to do if you experience high blood sugar:
► If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.

► These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store Actrapid

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 cartridge label and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening: Store in a refrigerator at 2°C – 8°C. Keep away from the cooling element. Do not freeze. If there are 6 months or more until the expiry date, the product may be stored outside of the refrigerator (below 30°C) for up to 4 weeks before it is taken into use or carried as a spare. Always keep the cartridge in the outer carton when you are not using it, in order to protect from light. The product must not be returned to the refrigerator after it has been stored outside of the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

During use or when carried as a spare: Do not refrigerate or freeze. You can carry it with you and keep it at room temperature (below 30°C) for up to 6 weeks.
Always keep the cartridge in the outer carton when you are not using it, in order to protect from light.

Discard the needle after each injection.

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 Actrapid contains

– The active substance is human insulin. Each ml contains 100 IU of human insulin. Each cartridge contains 300 IU of human insulin in 3 ml solution for injection.
– The other ingredients are zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

What Actrapid looks like and contents of the pack

Actrapid is presented as a solution for injection.
Pack sizes of 1, 5 and 10 cartridges of 3 ml. Not all pack sizes may be marketed.

The solution is clear and colourless.

Scientific Opinion Holder and Manufacturer

Scientific Opinion Holder

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

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:
– If the second and third characters are S6, P5, K7, R7, VG, FG or ZF, the manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

– If the second and third characters are H7 or T6, the manufacturer is Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France.

This leaflet was last revised in

Other sources of information

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

Package leaflet: Information for the user

Actrapid FlexPen 100 IU/ml (international units/ml) solution for injection in pre-filled pen
human insulin

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. See section 4.

What is in this leaflet

1. What Actrapid is and what it is used for

Actrapid is human insulin with a fast-acting effect.

Actrapid is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Treatment with Actrapid helps to prevent complications from your diabetes.

Actrapid will start to lower your blood sugar about half an hour after you inject it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with intermediate-acting or long-acting insulin preparations.

2. What you need to know before you use Actrapid

Do not use Actrapid

- ► If you are allergic to human insulin or any of the other ingredients in this medicine, see section 6.
- ► If you suspect hypoglycaemia (low blood sugar) is starting, see Summary of serious and very common side effects in section 4.
- ► In insulin infusion pumps.
- ► If FlexPen is dropped, damaged or crushed.
- ► If it has not been stored correctly or if it has been frozen, see section 5.
- ► If the insulin does not appear clear and colourless.

If any of these apply, do not use Actrapid. Talk to your doctor, pharmacist or nurse for advice.

Before using Actrapid

- ► Check the label to make sure it is the right type of insulin.
- ► Always use a new needle for each injection to prevent contamination.
- ► Needles and Actrapid FlexPen must not be shared.

► Actrapid FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Consult your doctor:
► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
► If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
► If you are ill, carry on taking your insulin and consult your doctor.
► If you are going abroad, travelling over time zones may affect your insulin needs and the timing hereof.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and Actrapid

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines affect your blood sugar level, and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormone (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes 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).

If you have taken any of the medicines listed here, tell your doctor, pharmacist or nurse.

Actrapid with alcohol

► If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding

► If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Actrapid can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
► There are no restrictions on treatment with Actrapid during breast-feeding.

Ask your doctor, pharmacist or nurse for advice before taking this medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Actrapid contains sodium

Actrapid contains less than 1 mmol sodium (23 mg) per dose, i.e. Actrapid is essentially 'sodium-free'.

3. How to use Actrapid

Dose and when to take your insulin

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection to avoid low blood sugar.

Do not change your insulin unless your doctor tells you to. 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.

Use in children and adolescents

Actrapid can be used in children and adolescents.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject

Actrapid is administered by injection under the skin (subcutaneously). You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). Actrapid FlexPen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting, see section 4. The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. The insulin will work more quickly if you inject into the waist (abdomen). You should always measure your blood sugar regularly.

How to handle Actrapid FlexPen

Actrapid FlexPen is a pre-filled disposable pen containing human insulin.

Read carefully the Instructions on how to use Actrapid FlexPen included in this package leaflet. You must use the pen as described in the Instructions on how to use Actrapid FlexPen.

Always ensure you use the correct pen before you inject your insulin.

If you take more insulin than you should
If you take too much insulin your blood sugar gets too low (hypoglycaemia). See Summary of serious and very common side effects in section 4.

If you forget to take your insulin

If you forget to take your insulin your blood sugar may get too high (hyperglycaemia). See Effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.

- Drink alcohol, see Actrapid with alcohol in section 2.

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. 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 sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
- ► If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- ► When the symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.
- ► If you have such low blood sugar that it makes you pass out, if you have had the need for an injection of glucagon, or if you have experienced many incidents of low blood sugar, talk to a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (becoming unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink, because you may choke.

Serious allergic reaction to Actrapid or one of its ingredients (called a systemic allergic reaction) is a very rare side effect, but it can potentially be life threatening. It may affect less than 1 in 10,000 people.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.
- ► If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect less than 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

List of other side effects

Uncommon side effects
May affect less than 1 in 100 people.

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of taking your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Very rare side effects
May affect less than 1 in 10,000 people.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop taking insulin.
- Repeatedly inject less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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 (acetone) smell of the breath.

What to do if you experience high blood sugar:
- ► If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- ► These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store Actrapid

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 FlexPen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening: Store in a refrigerator at 2°C – 8°C. Keep away from the cooling element. Do not freeze. If there are 6 months or more until the expiry date, the product may be stored outside of the refrigerator (below 30°C) for up to 4 weeks before it is taken into use or carried as a spare. Always keep the pen cap on your FlexPen when you are not using it, in order to protect from light. The product must not be returned to the refrigerator after it has been stored outside of the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

During use or when carried as a spare: Do not refrigerate or freeze. You can carry it with you and keep it at room temperature (below 30°C) for up to 6 weeks.

Always keep the pen cap on your FlexPen when you are not using it, in order to protect from light.

Discard the needle after each injection.

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 Actrapid contains

- The active substance is human insulin. Each ml contains 100 IU of human insulin. Each pre-filled pen contains 300 IU of human insulin in 3 ml solution for injection.
- The other ingredients are zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

What Actrapid looks like and contents of the pack

Actrapid is presented as a solution for injection.
Pack sizes of 1, 5 and 10 pre-filled pens of 3 ml. Not all pack sizes may be marketed.

The solution is clear and colourless.

Scientific Opinion Holder and Manufacturer

Scientific Opinion Holder

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

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are S6, P5, K7, R7, VG, FG or ZF, the manufacturer is Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

- If the second and third characters are H7 or T6, the manufacturer is Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France.

This leaflet was last revised in

Other sources of information

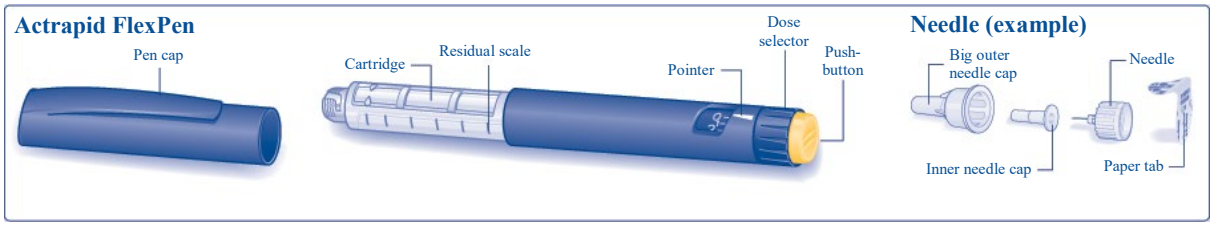
Detailed information on this medicine is available on the European Medicines Agency website http://www.ema.europa.eu.

Now turn over for information on how to use your FlexPen.

Instructions on how to use Actrapid solution for injection in FlexPen.

Read the following instructions carefully before using your FlexPen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your FlexPen is a pre-filled dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. FlexPen is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



Caring for your pen

Your FlexPen must be handled with care.If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

You can clean the exterior of your FlexPen by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your FlexPen. Once empty, it must be disposed of.

Preparing your Actrapid FlexPen

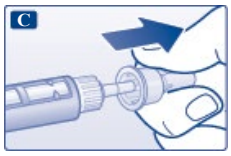
Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

A
Pull off the pen cap (see **A**).

B
Remove the paper tab from a new disposable needle.

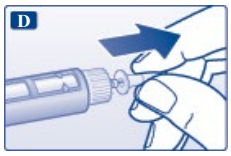
Screw the needle straight and tightly onto your FlexPen.

C
Pull off the big outer needle cap and keep it for later.



D
Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.

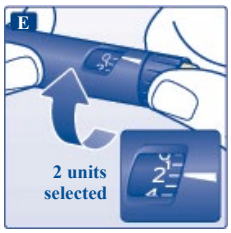


⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

⚠ Be careful not to bend or damage the needle before use.

Checking the insulin flow

E
Prior to each injection small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:
Turn the dose selector to select 2 units.



F
Hold your FlexPen with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.

G
Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If a drop of insulin still does not appear, the pen is defective, and you must use a new one.

⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.

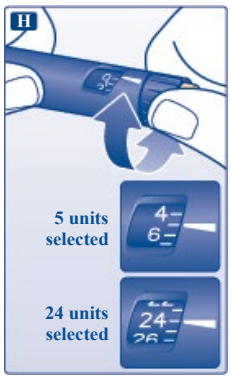
⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Selecting your dose

H
Check that the dose selector is set at 0.
Turn the dose selector to select the number of units you need to inject.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.



⚠ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.

⚠ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Making the injection

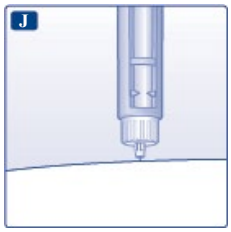
I
Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.
Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.

J
Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose.

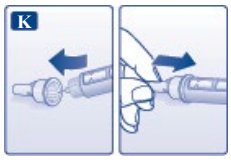
Withdraw the needle from the skin, then release the pressure on the push-button.

Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



K
Lead the needle into the big outer needle cap without touching it. When the needle is covered, carefully push the big outer needle cap completely on and then unscrew the needle.

Dispose of it carefully and put the pen cap back on.



⚠ Always remove the needle after each injection and store your FlexPen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

⚠ Caregivers must be very careful when handling used needles - to reduce the risk of needle sticks and cross-infection.

⚠ Dispose of your used FlexPen carefully without the needle attached.

⚠ Never share your pen or your needles with other people. It might lead to cross-infection.

⚠ Never share your pen with other people. Your medicine might be harmful to their health.

⚠ Always keep your pen and needles out of sight and reach of others, especially children.