1. **NAME OF THE MEDICINAL PRODUCT**

Actrapid 40 IU/ml solution for injection in a vial.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

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

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

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection in a vial.

Clear, colourless, aqueous solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of diabetes mellitus.

4.2 **Posology and method of administration**

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

**Dosage**

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

**Dosage adjustment**

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

Renal or hepatic impairment may reduce insulin requirement.

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

**Administration**
For subcutaneous or intravenous use. Actrapid may also be administered intravenously, which should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

The vials are for use with insulin syringes with a corresponding unit scale. When two types of insulin are mixed, draw the amount of fast-acting insulin first, followed by the amount of long-acting insulin.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Hypoglycaemia.

4.4 Special warnings and precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia. Usually, the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.

In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9).

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

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

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.
Before travelling between different time zones, the patient should be advised to consult the physician, since this may mean that the patient has to take insulin and meals at different times.

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

Actrapid contains metacresol, which may cause allergic reactions.

**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.

**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 physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

**The following substances may reduce insulin requirement:**

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

**The following substances may increase insulin requirement:**

- Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

**4.6 Pregnancy and lactation**

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death in utero. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

After delivery, insulin requirements return rapidly to pre-pregnancy values.

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

**4.7 Effects on ability to drive and use machines**
The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon (\(\geq 1/1,000\) to \(<1/100\)). Isolated spontaneous cases are presented as very rare defined as \(<1/10,000\), including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune system disorders
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.
4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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 \( t_{1/2} \) is therefore a measure of the absorption rather than of the elimination \textit{per se} of insulin from plasma (insulin in the blood stream has a \( t_{1/2} \) of a few minutes). Trials have indicated a \( t_{1/2} \) of about 2-5 hours.

Children and adolescents
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 \( C_{\text{max}} \), 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.

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 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 sulphites.

6.3 Shelf life
30 months when stored between 2°C - 8°C.
4 weeks when used or stored at room temperature (below 25°C).

6.4 Special precautions for storage
Before use: store in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.

During use: do not refrigerate. Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.
Protect from excessive heat and sunlight.
6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Insulin preparations which have been frozen must not be used.
Insulin solutions should not be used if they do not appear water clear and colourless.
Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/001-002, 016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Actrapid 100 IU/ml solution for injection in a vial

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

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

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

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection in a vial.

Clear, colourless, aqueous solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of diabetes mellitus.

4.2 **Posology and method of administration**

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

**Dosage**

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

**Dosage adjustment**

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

Renal or hepatic impairment may reduce insulin requirement.

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

**Administration**
For subcutaneous or intravenous use. Actrapid may also be administered intravenously, which should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

The vials are for use with insulin syringes with a corresponding unit scale. When two types of insulin are mixed, draw the amount of fast-acting insulin first, followed by the amount of long-acting insulin.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Hypoglycaemia.

4.4 Special warnings and precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia.

Usually, the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.

In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

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

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.
Before travelling between different time zones, the patient should be advised to consult the physician, since this may mean that the patient has to take insulin and meals at different times.

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

Actrapid contains metacresol, which may cause allergic reactions.

**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.

**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 physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

**The following substances may reduce insulin requirement:**

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

**The following substances may increase insulin requirement:**

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

**4.6 Pregnancy and lactation**

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

After delivery, insulin requirements return rapidly to pre-pregnancy values.

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

**4.7 Effects on ability to drive and use machines**
The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon - Refraction disorders
Refractive anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune system disorders
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.
4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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 (t½) 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 t½ of a few minutes). Trials have indicated a t½ of about 2-5 hours.

Children and adolescents
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 Cmax, 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.

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 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 sulphites.

6.3 Shelf life
30 months when stored between 2°C - 8°C.
6 weeks when used or stored at room temperature (below 25°C)

6.4 Special precautions for storage
Before use: store in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.

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

Keep the vial in the outer carton in order to protect from light.
Protect from excessive heat and sunlight.
6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Insulin preparations which have been frozen must not be used. Insulin solutions should not be used if they do not appear water clear and colourless. Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/003-004, 017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Actrapid Penfill 100 IU/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1 ml contains 100 IU of insulin human.
1 cartridge contains 3 ml equivalent to 300 IU.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

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

Dosage
Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

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

Renal or hepatic impairment may reduce insulin requirement.

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

Administration
For subcutaneous use. The intravenous use of Actrapid from any pen or cartridge should be an exception only in situations where vials are not available. In this case Actrapid should be drawn into an insulin syringe, provided air is avoided, or infused with an infusion system. This procedure should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

The cartridges are designed to be used with Novo Nordisk delivery systems (durable devices for repeated use) and NovoFine or NovoTwist needles. Detailed instruction accompanying the delivery system must be followed.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Hypoglycaemia.

4.4 Special warnings and precautions for use

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

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

As with any insulin therapy, injection site reactions may occur and include pain, itching, hives, swelling and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Actrapid
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

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

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

Actrapid contains metacresol, which may cause allergic reactions.

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.

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 physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

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

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

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death in utero. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy values.

Insulin treatment of the nursing mother presents no risk to the baby. However, the Actrapid dosage may need to be adjusted.
4.7 Effects on ability to drive and use machines

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune system disorders
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

4.9 Overdose

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

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

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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 $t_{1/2}$ 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 $t_{1/2}$ of a few minutes). Trials have indicated a $t_{1/2}$ of about 2-5 hours.

Children and adolescents
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.

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 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 sulphites.

6.3 Shelf life
30 months when stored between 2°C - 8°C.
6 weeks when used or carried as a spare (below 30°C).

6.4 Special precautions for storage
Before use: store in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.
During use: do not refrigerate. Do not store above 30°C.
Keep the cartridge in the outer carton in order to protect from light.
Protect from excessive heat and sunlight.

6.5 Nature and contents of container

3 ml glass cartridge (type 1) with a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper.
Pack sizes: 1, 5 and 10 cartridges x 3 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Cartridges should only be used in combination with products that are compatible with them and allow the cartridge to function safely and effectively.

Actrapid Penfill is for single person use only. The container must not be refilled.

Insulin preparations which have been frozen must not be used.
Insulin solutions should not be used if they do not appear water clear and colourless.
Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/005-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT
Actrapid NovoLet 100 IU/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Insulin human, rDNA (produced by recombinant DNA technology in Saccharomyces cerevisiae).

1 ml contains 100 IU of insulin human.
1 pre-filled pen contains 3 ml equivalent to 300 IU.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection in a pre-filled pen.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of diabetes mellitus.

4.2 Posology and method of administration
Actrapid is a fast-acting insulin and may be used in combination with long-acting insulin products.

Dosage
Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

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

Renal or hepatic impairment may reduce insulin requirement.

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

Administration
For subcutaneous use. The intravenous use of Actrapid from any pen or cartridge should be an exception only in situations where vials are not available. In this case Actrapid should be drawn into an insulin syringe, provided air is avoided, or infused with an infusion system. This procedure should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Actrapid NovoLet is designed to be used with NovoFine needles. NovoLet delivers 2-78 units in increments of 2 units. The pens should be primed before injection so that the dose selector returns to zero and a drop of insulin appears at the needle top. The dose is set by turning the selector, which returns to zero during the injection.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Hypoglycaemia.

4.4 Special warnings and precautions for use

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

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

As with any insulin therapy, injection site reactions may occur and include pain, itching, hives, swelling and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Actrapid.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

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

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

Actrapid contains metacresol, which may cause allergic reactions.

**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.

### 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 physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

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

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

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

### 4.6 Pregnancy and lactation

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

After delivery, insulin requirements return rapidly to pre-pregnancy values.
Insulin treatment of the nursing mother presents no risk to the baby. However, the Actrapid dosage may need to be adjusted.

4.7 Effects on ability to drive and use machines

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders

Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders

Uncommon - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders

Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions

Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune system disorders

Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

4.9 Overdose

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patients carry some sugar lumps, sweets, biscuits or sugary fruit juice.

- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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 ($t_{1/2}$) 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 $t_{1/2}$ of a few minutes). Trials have indicated a $t_{1/2}$ of about 2-5 hours.

**Children and adolescents**

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.

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 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 sulphites.

6.3 Shelf life

30 months when stored between $2^\circ$C - $8^\circ$C.

6 weeks when used or carried as a spare (below $30^\circ$C).

6.4 Special precautions for storage

Before use: store in a refrigerator ($2^\circ$C - $8^\circ$C).

Do not store them in or too near the freezer section or cooling element.

Do not freeze.

During use: do not refrigerate. Do not store above $30^\circ$C.
Keep the pen cap on in order to protect from light. 
Protect from excessive heat and sunlight.

6.5 Nature and contents of container

Pre-filled pen (multidose disposable pen) comprising a pen injector with a cartridge (3 ml). The cartridge is made of glass (type 1), containing a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. The pen injector is made of plastic.
Pack sizes: 5 and 10 pre-filled pens x 3 ml. 
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Pens should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

Actrapid NovoLet is for single person use only. The container must not be refilled.

Insulin preparations which have been frozen must not be used.
Insulin solutions should not be used if they do not appear water clear and colourless.
Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/008-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Actrapid InnoLet 100 IU/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1 ml contains 100 IU of insulin human.
1 pre-filled pen contains 3 ml equivalent to 300 IU.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

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

**Dosage**

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

**Dosage adjustment**

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

Renal or hepatic impairment may reduce insulin requirement.

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

**Administration**
For subcutaneous use. The intravenous use of Actrapid from any pen or cartridge should be an exception only in situations where vials are not available. In this case Actrapid should be drawn into an insulin syringe, provided air is avoided, or infused with an infusion system. This procedure should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Actrapid InnoLet is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. InnoLet delivers 1-50 units in increments of 1 unit. The patient should be advised not to use any counterfeit needles. The pens should be primed before injection so that the dose selector returns to zero and a drop of insulin appears at the needle top. The dose is set by turning the selector, which returns to zero during the injection.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Hypoglycaemia.

4.4 Special warnings and precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia.

Usually, the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.

In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

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

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

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

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

Actrapid contains metacresol, which may cause allergic reactions.

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.

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 physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

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

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

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death in utero. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

After delivery, insulin requirements return rapidly to pre-pregnancy values.
Insulin treatment of the nursing mother presents no risk to the baby. However, the Actrapid dosage may need to be adjusted.

4.7 Effects on ability to drive and use machines

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

**Immune system disorders**
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

4.9 Overdose

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

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

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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

34
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 \( t_{1/2} \) 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 \( t_{1/2} \) of a few minutes). Trials have indicated a \( t_{1/2} \) of about 2-5 hours.

**Children and adolescents**
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 \( C_{\text{max}} \), 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.

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 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 sulphites.

6.3 Shelf life
- 30 months when stored between 2°C - 8°C.
- 6 weeks when used or carried as a spare (below 30°C).

6.4 Special precautions for storage
Before use: store in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.

During use: do not refrigerate. Do not store above 30°C.
Keep the pen cap on in order to protect from light.
Protect from excessive heat and sunlight.

6.5 Nature and contents of container

Pre-filled pen (multidose disposable pen) comprising a pen injector with a cartridge (3 ml). The cartridge is made of glass (type 1), containing a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. The pen injector is made of plastic.
Pack sizes: 1, 5 and 10 pre-filled pens x 3 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Pens should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

Actrapid InnoLet is for single person use only. The container must not be refilled.

Insulin preparations which have been frozen must not be used.
Insulin solutions should not be used if they do not appear water clear and colourless.
Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/010-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Actrapid FlexPen 100 IU/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin human, rDNA (produced by recombinant DNA technology in \textit{Saccharomyces cerevisiae}).

1 ml contains 100 IU of insulin human.
1 pre-filled pen contains 3 ml equivalent to 300 IU.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

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

\textbf{Dosage}

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

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

\textbf{Dosage adjustment}

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

Renal or hepatic impairment may reduce insulin requirement.

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

\textbf{Administration}
For subcutaneous use. The intravenous use of Actrapid from any pen or cartridge should be an exception only in situations where vials are not available. In this case Actrapid should be drawn into an insulin syringe, provided air is avoided, or infused with an infusion system. This procedure should only be carried out by health care professionals.

Actrapid is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

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. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Actrapid FlexPen is designed to be used with NovoFine short cap needles of 8 mm or shorter in length. The needle box is marked with an S. FlexPen delivers 1-60 units in increments of 1 unit. The pens should be primed before injection so that the dose selector returns to zero and a drop of insulin appears at the needle top. The dose is set by turning the selector, which returns to zero during the injection.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Hypoglycaemia.

4.4 Special warnings and precautions for use

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

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Actrapid, it may occur with the first dose or during the first several weeks or months.

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

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

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

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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.

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

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

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

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

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

**4.6 Pregnancy and lactation**

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

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

After delivery, insulin requirements return rapidly to pre-pregnancy values.
Insulin treatment of the nursing mother presents no risk to the baby. However, the Actrapid dosage may need to be adjusted.

4.7 Effects on ability to drive and use machines

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Actrapid, are listed below. The frequencies are defined as: uncommon ($\geq$1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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

Skin and subcutaneous tissue disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune system disorders
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

4.9 Overdose

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

• Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patients carry some sugar lumps, sweets, biscuits or sugary fruit juice.

• Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


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 dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin 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 ($t_{1/2}$) 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 $t_{1/2}$ of a few minutes). Trials have indicated a $t_{1/2}$ of about 2-5 hours.

**Children and adolescents**
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 $C_{\text{max}}$, 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.

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 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 sulphites.

6.3 Shelf life

30 months when stored between 2°C - 8°C.

6 weeks when used or carried as a spare (below 30°C).

6.4 Special precautions for storage

Before use: store in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.

During use: do not refrigerate. Do not store above 30°C.
Keep the pen cap on in order to protect from light.
Protect from excessive heat and sunlight.

6.5 Nature and contents of container

Pre-filled pen (multidose disposable pen) comprising a pen injector with a cartridge (3 ml). The cartridge is made of glass (type 1), containing a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. The pen injector is made of plastic.
Pack sizes: 1, 5 and 10 pre-filled pens x 3 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intravenous use, infusion systems with Actrapid at concentrations 0.05 IU/ml - 1.0 IU/ml insulin human in the following infusion fluids; 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 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 absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Pens should only be used in combination with products that are compatible with them and allow the pens to function safely and effectively.

Actrapid FlexPen is for single person use only. The container must not be refilled.

Insulin preparations which have been frozen must not be used.
Insulin solutions should not be used if they do not appear water clear and colourless.
Actrapid should not be used in insulin pumps for continuous subcutaneous insulin infusion.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/013-015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: October 2002
Date of latest renewal: 18 September 2007

10. DATE OF REVISION OF THE TEXT
ANNEX II

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

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

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

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

Name and address of the manufacturers responsible for batch release

Actrapid, Actrapid NovoLet, Actrapid InnoLet:

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

Actrapid Penfill and FlexPen:

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

Novo Nordisk Production SAS
45, Avenue d’Orléans
F-28002 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 OF THE MARKETING AUTHORISATION

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

Medicinal product subject to medical prescription

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.0 (06 March 2009) of the Risk Management Plan
(RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Actrapid 40 IU/ml solution for injection in a vial
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 40 IU (1.4 mg) of insulin human (rDNA).

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 x 10 ml
5 x 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP/
During use: use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light
During use: do not refrigerate or store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/001 1 x 10 ml
EU/1/02/230/002 5 x 10 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid 40
### Minimum Particulars to Appear on Small Immediate Packaging Units

#### Vial Label

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product and Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actrapid 40 IU/ml solution for injection</td>
</tr>
<tr>
<td>Insulin human (rDNA)</td>
</tr>
<tr>
<td>SC, IV use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Method of Administration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP/</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Batch Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Contents by Weight, by Volume or by Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novo Nordisk A/S</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT
Actrapid 100 IU/ml solution for injection in a vial
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE
1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

3. LIST OF EXCipients
zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS
Solution for injection
1 x 10 ml
5 x 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Subcutaneous or intravenous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP/
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light
During use: do not refrigerate or store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/003  1 x 10 ml
EU/1/02/230/004  5 x 10 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

1 vial of 10 ml contains 1000 IU

16. INFORMATION IN BRAILLE

Actrapid 100
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL LABEL**

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**
   
   Actrapid 100 IU/ml solution for injection
   Insulin human (rDNA)
   SC, IV use

2. **METHOD OF ADMINISTRATION**

3. **EXPIRY DATE**
   
   EXP/

4. **BATCH NUMBER**
   
   Batch:

5. **CONTENT BY WEIGHT, BY VOLUME OR BY UNIT**
   
   10 ml
   1 vial of 10 ml contains 1000 IU

6. **OTHER**
   
   Novo Nordisk A/S
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Actrapid 40 IU/ml solution for injection in a vial
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 40 IU (1.4 mg) of insulin human (rDNA).

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 x 10 ml
This is part of a multipack and not for sale of individual vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP/
During use: use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light
During use: do not refrigerate or store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/016

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid 40
### PARTICULARS TO APPEAR ON THE PACKAGING

#### OUTER WRAPPER LABEL ON MULTIPACKS

#### 1. NAME OF THE MEDICINAL PRODUCT

Actrapid 40 IU/ml solution for injection in a vial
Insulin human (rDNA)

#### 2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 40 IU (1.4 mg) of insulin human (rDNA).

#### 3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

#### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 x (1 x 10 ml)
This is a multipack and not for sale of individual vials

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

#### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

#### 8. EXPIRY DATE

EXP/
During use: use within 4 weeks

#### 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light
During use: do not refrigerate or store above 25°C
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/016

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE


16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Actrapid 100 IU/ml solution for injection in a vial
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 x 10 ml
This is part of a multipack and not for sale of individual vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP/
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light
During use: do not refrigerate or store above 25°C

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/230/017

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

1 vial of 10 ml contains 1000 IU

16. **INFORMATION IN BRAILLE**

Actrapid 100
### PARTICULARS TO APPEAR ON THE PACKAGING OUTHER WRAPPER LABEL ON MULTIPACKS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actrapid 100 IU/ml solution for injection in a vial</td>
</tr>
<tr>
<td>Insulin human (rDNA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection</td>
</tr>
<tr>
<td>5 x (1 x 10 ml)</td>
</tr>
<tr>
<td>This is a multipack and not for sale of individual vials</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous or intravenous use</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP/</td>
</tr>
<tr>
<td>During use: use within 6 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in a refrigerator (2°C - 8°C)</td>
</tr>
<tr>
<td>Do not freeze</td>
</tr>
<tr>
<td>Keep the vial in the outer carton in order to protect from light</td>
</tr>
<tr>
<td>During use: do not refrigerate or store above 25°C</td>
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<tr>
<td>Section</td>
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<tr>
<td>15.</td>
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<td></td>
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<tr>
<td>16.</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Actrapid Penfill 100 IU/ml solution for injection in a cartridge
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 x 3 ml
5 x 3 ml
10 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Penfill cartridges for use with Novo Nordisk insulin devices
Read the package leaflet before use
Actrapid Penfill is for use by one person only

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP/
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the cartridge in the outer carton in order to protect from light
During use: do not refrigerate or store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/005 1 x 3 ml
EU/1/02/230/006 5 x 3 ml
EU/1/02/230/007 10 x 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid Penfill
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

#### PENFILL LABEL

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

Actrapid Penfill 100 IU/ml solution for injection
Insulin human (rDNA)
SC use

**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 AND THE IMMEDIATE PACKAGING

**OUTER CARTON**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actrapid NovoLet 100 IU/ml solution for injection in a pre-filled pen</td>
</tr>
<tr>
<td>Insulin human (rDNA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection</td>
</tr>
<tr>
<td>5 x 3 ml</td>
</tr>
<tr>
<td>10 x 3 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use</td>
</tr>
<tr>
<td>Actrapid NovoLet is designed to be used with NovoFine needles</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
<tr>
<td>Actrapid NovoLet is for use by one person only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
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<table>
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<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP/</td>
</tr>
<tr>
<td>During use: use within 6 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in a refrigerator (2°C - 8°C)</td>
</tr>
</tbody>
</table>
Do not freeze
Protect from light
During use: do not refrigerate or store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/008  5 x 3 ml
EU/1/02/230/009  10 x 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid NovoLet
| MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS |
| NOVOLET LABEL |

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

Actrapid NovoLet 100 IU/ml solution for injection  
Insulin human (rDNA)  
SC use

**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 AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Actrapid InnoLet 100 IU/ml solution for injection in a pre-filled pen
Insulin human (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

3. LIST OF EXCIPIENTS

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

   | 1 x 3 ml |
---|----------|
 5 | 5 x 3 ml |
10 | 10 x 3 ml |

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

Read the package leaflet before use

Actrapid InnoLet is for use by one person only

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP/
During use: use within 6 weeks

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator (2°C - 8°C)
Do not freeze
Protect from light
During use: do not refrigerate or store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/010  1 x 3 ml
EU/1/02/230/011  5 x 3 ml
EU/1/02/230/012  10 x 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid InnoLet
## MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

### INNOLET LABEL

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td>Actrapid InnoLet 100 IU/ml solution for injection</td>
<td>Insulin human (rDNA)</td>
</tr>
<tr>
<td></td>
<td>SC use</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td></td>
</tr>
<tr>
<td>EXP/</td>
<td></td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td></td>
</tr>
<tr>
<td>Batch:</td>
<td></td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td></td>
</tr>
<tr>
<td>3 ml</td>
<td></td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk A/S</td>
<td></td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>OUTER CARTON</td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Actrapid FlexPen 100 IU/ml solution for injection in a pre-filled pen 
Insulin human (rDNA)

2. **STATEMENT OF ACTIVE SUBSTANCE**

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

3. **LIST OF EXCIPIENTS**

zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection  
1 x 3 ml  
5 x 3 ml  
10 x 3 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use  
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.  
Needles are not includedRead the package leaflet before use  
Actrapid FlexPen is for use by one person only

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

Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP/  
During use: use within 6 weeks

9. **SPECIAL STORAGE CONDITIONS**
Store in a refrigerator (2°C - 8°C)
Do not freeze
Protect from light
During use: do not refrigerate or store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/230/013  1 x 3 ml
EU/1/02/230/014  5 x 3 ml
EU/1/02/230/015  10 x 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Actrapid FlexPen
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**FLEXPEN LABEL**

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**
   
   Actrapid FlexPen 100 IU/ml solution for injection  
   Insulin human (rDNA)  
   SC use  

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
Read all of this leaflet carefully before you start using your insulin.

– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, diabetes nurse or your pharmacist.
– This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
– If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or your pharmacist.

1. WHAT ACTRAPID IS AND WHAT IT IS USED FOR

Actrapid is human insulin to treat diabetes. Actrapid is a fast-acting insulin. This means that it will start to lower your blood sugar about half an hour after you take it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with longer-acting insulin products.

2. BEFORE YOU USE ACTRAPID

Do not use Actrapid

► If you are allergic (hypersensitive) to this insulin product, metacresol or any of the other ingredients (see 7 Further information). Look out for the signs of allergy in 5 Possible side effects
► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 What to do in an emergency for more about hypos.

Take special care with Actrapid

► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
► If you are drinking alcohol: watch for signs of a hypo and never drink alcohol on an empty stomach
► If you are exercising more than usual or if you want to change your usual diet
► If you are ill: carry on taking your insulin
► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections.

Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed. Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

Pioglitazone (oral antidiabetic medicine used for the treatment of type 2 diabetes mellitus)
Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).
Pregnancy and breast-feeding

If you are pregnant, planning a pregnancy or breast-feeding: please contact your doctor for advice.

Driving and using machines

If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

3. HOW TO USE ACTRAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.
Eat a meal or snack containing carbohydrates within 30 minutes of the injection.
It is recommended that you measure your blood glucose regularly.

Before using Actrapid

► Check the label to make sure it is the right type of insulin
► Disinfect the rubber membrane with a medicinal swab.

Do not use Actrapid

► In insulin infusion pumps
► If the protective cap is loose or missing. Each vial has a protective, tamper-proof plastic cap.
  If it isn’t in perfect condition when you get the vial, return the vial to your supplier
► If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
► If it does not appear water clear and colourless.

How to use this insulin

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.
Actrapid vials are for use with insulin syringes with the corresponding unit scale.
Actrapid may also be administered intravenously in special situations by medical professionals.

To inject Actrapid on its own

1. Draw air into the syringe, in the same amount as the dose of insulin you need
2. Inject the air into the vial: push the needle through the rubber stopper and press the plunger
3. Turn the vial and syringe upside down
4. Draw the right dose of insulin into the syringe
5. Pull the needle out of the vial
6. Make sure there is no air left in the syringe: point the needle upwards and push the air out
7. Check you have the right dose
8. Inject straight away.

To mix Actrapid with long-acting insulin
1. Roll the vial of long-acting insulin between your hands. Do this until the liquid is uniformly white and cloudy.
2. Draw as much air into the syringe as the dose of long-acting insulin you need. Inject the air into the long-acting insulin vial, then pull out the needle.
3. Draw as much air into the syringe as the dose of Actrapid you need. Inject the air into the Actrapid vial. Then turn the vial and syringe upside down.
4. Draw the right dose of Actrapid into the syringe. Pull the needle out of the vial. Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose.
5. Now push the needle into the vial of long-acting insulin.
6. Then turn the vial and syringe upside down.
7. Draw the right dose of long-acting insulin into the syringe.
8. Pull the needle out of the vial.
9. Make sure there is no air left in the syringe, and check the dose.
10. Inject the mixture straight away.

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

Inject the insulin

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

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo

A hypo means your blood sugar level is too low.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you get any of these signs, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don’t take any insulin if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

- If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon

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

Causes of a hypo
You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

**If your blood sugar gets too high**

Your blood sugar may get too high (this is called hyperglycaemia). **The warning signs** appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

**If you get any of these signs**, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

**Causes of hyperglycaemia**

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

**5. POSSIBLE SIDE EFFECTS**

Like all medicines, Actrapid can cause side effects, although not everybody gets them. Actrapid may cause hypoglycaemia (low blood sugar). See the advice in 4 What to do in an emergency.

**Side effects reported uncommonly** (in less than 1 patient in 100)

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

**Changes at the injection site (Lipodystrophy).** If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or diabetes nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

**Signs of allergy.** Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

**Seek medical advice immediately:**

- if signs of allergy spread to other parts of the body, or
- if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

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

**Painful neuropathy** (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

**Swollen joints.** When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.
Side effects reported very rarely (in less than 1 patient in 10,000)

Diabetic retinopathy (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or pharmacist.

6. HOW TO STORE ACTRAPID

Keep out of the reach and sight of children.

Do not use Actrapid after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

The vials that are not being used are to be stored in a refrigerator (2°C - 8°C).
Do not store them in or too near the freezer section or cooling element.
Do not freeze.
Keep the vials in the original package.

The vials that are being used or about to be used are not to be kept in a refrigerator. You can carry them with you and keep them at room temperature (not above 25ºC) for up to 4 weeks.
Always keep the vial in the outer carton when you’re not using it in order to protect it from light.
Actrapid must be protected from excessive heat and sunlight.

Actrapid should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

What Actrapid contains

– The active substance is insulin human made by recombinant biotechnology. 1 ml contains 40 IU of insulin human. 1 vial contains 10 ml equivalent to 400 IU
– 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
The solution for injection comes as a clear, colourless, aqueous solution.
It is supplied in packs of 1 or 5 vials of 10 ml or in a multipack of 5 x (1 x 10 ml) vials. Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last approved in
Read all of this leaflet carefully before you start using your insulin.

– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, diabetes nurse or your pharmacist.
– This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
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► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 What to do in an emergency for more about hypos.

Take special care with Actrapid

► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
► If you are drinking alcohol: watch for signs of a hypo and never drink alcohol on an empty stomach
► If you are exercising more than usual or if you want to change your usual diet
► If you are ill: carry on taking your insulin
► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections.

Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

Pioglitazone (oral antidiabetic medicine used for the treatment of type 2 diabetes mellitus)
Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).
Pregnancy and breast-feeding

If you are pregnant, planning a pregnancy or breast-feeding: please contact your doctor for advice.

Driving and using machines

If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

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Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.
Eat a meal or snack containing carbohydrates within 30 minutes of the injection.
It is recommended that you measure your blood glucose regularly.

Before using Actrapid

- Check the label to make sure it is the right type of insulin
- Disinfect the rubber membrane with a medicinal swab.

Do not use Actrapid

- In insulin infusion pumps
- If the protective cap is loose or missing. Each vial has a protective, tamper-proof plastic cap.
  If it isn’t in perfect condition when you get the vial, return the vial to your supplier
- If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
- If it does not appear water clear and colourless.

How to use this insulin

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.
Actrapid vials are for use with insulin syringes with the corresponding unit scale.
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1. Roll the vial of long-acting insulin between your hands. Do this until the liquid is uniformly white and cloudy.

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3. Draw as much air into the syringe as the dose of Actrapid you need. Inject the air into the Actrapid vial. Then turn the vial and syringe upside down.

4. Draw the right dose of Actrapid into the syringe. Pull the needle out of the vial. Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose.

5. Now push the needle into the vial of long-acting insulin.

6. Then turn the vial and syringe upside down.

7. Draw the right dose of long-acting insulin into the syringe.

8. Pull the needle out of the vial.

9. Make sure there is no air left in the syringe, and check the dose.

10. Inject the mixture straight away.

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

Inject the insulin

► Inject the insulin under the skin. Use the injection technique advised by your doctor or diabetes nurse.

► Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo

A hypo means your blood sugar level is too low.

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Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

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► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

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Causes of a hypo
You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

**If your blood sugar gets too high**

Your blood sugar may get too high (this is called hyperglycaemia).

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

If you get any of these signs, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away. These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

**Causes of hyperglycaemia**

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
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## 5. POSSIBLE SIDE EFFECTS

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**Side effects reported uncommonly** (in less than 1 patient in 100)

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

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Seek medical advice immediately:

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It is recommended that you measure your blood glucose regularly.

Before using Actrapid

► Check the label to make sure it is the right type of insulin
► Always check the cartridge, including the rubber plunger (stopper). Don’t use it if any damage is seen or if there is a gap between the rubber plunger and the white label band. Take it back to your supplier. See your delivery system manual for further instructions
► Disinfect the rubber membrane with a medicinal swab
► Always use a new needle for each injection to prevent contamination.

Do not use Actrapid

► In insulin infusion pumps
► If Penfill or the device containing Penfill is dropped, damaged or crushed there is a risk of leakage of insulin
► If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
► If it does not appear water clear and colourless.

Do not refill Actrapid Penfill.
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.

How to use this insulin

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.

How to inject this insulin

► Inject the insulin under the skin. Use the injection technique advised by your doctor or diabetes nurse and described in your delivery system manual

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Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered.

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.

4. WHAT TO DO IN AN EMERGENCY

If you get a hypo

A hypo means your blood sugar level is too low. The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you get any of these signs, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don’t take any insulin if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

► If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death

► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon

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

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

• If you take too much insulin
• If you eat too little or miss a meal
• If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia). The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

If you get any of these signs, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

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

5. POSSIBLE SIDE EFFECTS

Like all medicines, Actrapid can cause side effects although not everybody gets them. Actrapid may cause hypoglycaemia (low blood sugar). See the advice in 4 What to do in an emergency.

Side effects reported uncommonly (in less than 1 patient in 100)

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

Changes at the injection site (Lipodystrophy). If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or diabetes nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

Signs of allergy. Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:
• if signs of allergy spread to other parts of the body, or
• if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

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

Painful neuropathy (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

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

Side effects reported very rarely (in less than 1 patient in 10,000)

Diabetic retinopathy (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or pharmacist.

6. HOW TO STORE ACTRAPID

Keep out of the reach and sight of children.

Do not use Actrapid after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

The Penfill that is not being used is to be stored in a refrigerator (2°C - 8°C). Do not store them in or too near the freezer section or cooling element.
Do not freeze.
Keep the Penfill in the original package.
**The Penfill that is being used** or about to be used is not to be kept in a refrigerator. You can carry it with you and keep it at room temperature (not above 30°C) for up to 6 weeks.
Always keep your cartridge in the outer carton when you’re not using it in order to protect it from light.
Actrapid must be protected from excessive heat and sunlight.

Actrapid should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. **FURTHER INFORMATION**

**What Actrapid contains**

- **The active substance** is insulin human made by recombinant biotechnology. 1 ml contains 100 IU of insulin human. 1 cartridge contains 3 ml equivalent to 300 IU

- **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**
The solution for injection comes as a clear, colourless, aqueous solution.
It is supplied in packs of 1, 5 or 10 cartridges of 3 ml. Not all packs may be marketed.

**Marketing Authorisation 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 W5, S6, P5, K7, or ZF Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark is the manufacturer

- If the second and third characters are H7 or T6 Novo Nordisk Production SAS, 45 Avenue d’Orléans F-28002 Chartres, France is the manufacturer.

**This leaflet was last approved in**
Read all of this leaflet carefully before you start using your insulin.

– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, diabetes nurse or your pharmacist.
– This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
– If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or your pharmacist.

This side of the leaflet:
1. What Actrapid is and what it is used for
2. Before you use Actrapid
3. How to use Actrapid
4. What to do in an emergency
5. Possible side effects
6. How to store Actrapid
7. Further information

Overleaf: How to use your NovoLet

1. WHAT ACTRAPID IS AND WHAT IT IS USED FOR

Actrapid is human insulin to treat diabetes. Actrapid is a fast-acting insulin. This means that it will start to lower your blood sugar about half an hour after you take it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with longer-acting insulin products.

2. BEFORE YOU USE ACTRAPID

Do not use Actrapid

► If you are allergic (hypersensitive) to this insulin product, metacresol or any of the other ingredients (see 7 Further information). Look out for the signs of allergy in 5 Possible side effects

► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 What to do in an emergency for more about hypos.

Take special care with Actrapid

► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands

► If you are drinking alcohol: watch for signs of a hypo and never drink alcohol on an empty stomach

► If you are exercising more than usual or if you want to change your usual diet

► If you are ill: carry on taking your insulin

► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections.

Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

Pioglitazone (oral antidiabetic medicine used for the treatment of type 2 diabetes mellitus)
Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Pregnancy and breast-feeding
If you are pregnant, planning a pregnancy or breast-feeding: please contact your doctor for advice.

Driving and using machines
If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

3. HOW TO USE ACTRAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.
Eat a meal or snack containing carbohydrates within 30 minutes of the injection.
It is recommended that you measure your blood glucose regularly.

Injecting insulin
See overleaf for detailed instructions.

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.

Do not use Actrapid
► In insulin infusion pumps
► If NovoLet is dropped, damaged or crushed there is a risk of leakage of insulin
► If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
► If it does not appear water clear and colourless.

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.

4. WHAT TO DO IN AN EMERGENCY
If you get a hypo

A hypo means your blood sugar level is too low.

**The warning signs of a hypo** may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

**If you get any of these signs**, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don't take any insulin if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death

► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon

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

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia).

**The warning signs** appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

**If you get any of these signs**, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

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

5. **POSSIBLE SIDE EFFECTS**
Like all medicines, Actrapid can cause side effects, although not everybody gets them. Actrapid may cause hypoglycaemia (low blood sugar). See the advice in 4 What to do in an emergency.

**Side effects reported uncommonly** (in less than 1 patient in 100)

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

**Changes at the injection site (Lipodystrophy).** If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or diabetes nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

**Signs of allergy.** Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

**Seek medical advice immediately:**
- if signs of allergy spread to other parts of the body, or
- if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

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

**Painful neuropathy** (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

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

**Side effects reported very rarely** (in less than 1 patient in 10,000)

**Diabetic retinopathy** (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or pharmacist.

### 6. HOW TO STORE ACTRAPID

Keep out of the reach and sight of children.

Do not use Actrapid after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

**The NovoLet that is not being used** is to be stored in a refrigerator (2°C - 8°C). Do not store them in or too near the freezer section or cooling element. Do not freeze.

**The NovoLet that is being used,** about to be used or carried as a spare is not to be kept in a refrigerator. You can carry it with you and keep it at room temperature (not above 30°C) for up to 6 weeks.

Always keep the pen cap on your NovoLet when you’re not using it in order to protect it from light. Actrapid must be protected from excessive heat and sunlight.
Actrapid should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

What Actrapid contains

- **The active substance** is insulin human made by recombinant biotechnology. 1 ml contains 100 IU of insulin human. 1 pre-filled pen contains 3 ml equivalent to 300 IU

- **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
The solution for injection comes as a clear, colourless, aqueous solution. It is supplied in packs of 5 or 10 pre-filled pens of 3 ml. Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer

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

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

This leaflet was last approved in
Information on how to use Actrapid NovoLet

Please read the following instructions carefully before using your Actrapid NovoLet.

Introduction

Actrapid NovoLet is a simple, compact pre-filled pen. You can dial doses from 2 to 78 units in increments of 2 units. Actrapid NovoLet is designed to be used with NovoFine needles. As a precautionary measure, always carry a spare insulin delivery device in case your NovoLet is lost or damaged.

Getting started

Check the label to make sure that your Actrapid NovoLet contains the correct type of insulin. Take off the pen cap.

• Disinfect the rubber membrane with a medicinal swab
• Always use a new needle for each injection to prevent contamination
• Remove the protective tab from a NovoFine needle
• Screw the needle straight and tightly onto Actrapid NovoLet (picture A)
• Pull off the big outer needle cap and the inner needle cap. Do not discard the big outer needle cap.

Priming to expel air

Small amounts of air may collect in the needle and cartridge during normal use. To avoid injection of air and ensure proper dosing:

• Hold Actrapid NovoLet with the needle pointing upwards
• Tap the cartridge gently with your finger a few times. Any air bubbles will collect at the top of the cartridge
• Keeping the needle upwards, turn the cartridge for one click in the direction of the arrow (picture B)
• Still with the needle upwards, press the push-button fully down (picture C)
• A drop of insulin must 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 device is defective and must not be used.

Setting the dose

• Put the cap back on the pen, with 0 next to the dosage indicator (picture D)
• Check that the push-button is fully down. If it isn’t, turn the cap until the push-button is fully depressed
• Hold your Actrapid NovoLet horizontally. Now you’re ready to set the dose you need
• Turn the cap in the direction of the arrow (picture E) to set the right dose. You’ll feel the cap clicking, and the push-button will rise up
• Don’t put your hand over the push-button when you set the dose. If the push-button cannot rise freely, some of your insulin will be pushed out of the needle
• The scale on the cap shows 0, 2, 4, 6, 8, 10, 12, 14, 16 and 18 units. For every click you feel when you turn the cap, you set 2 units more. The push-button also rises as you turn the cap
• The scale under the push-button shows 20, 40 and 60 units. Every time you fully turn the cap, you set 20 units.
Dosage examples

To set 8 units:
Turn the cap until 8 is opposite the dosage indicator; four clicks

To select 26 units:
Turn the cap round 1 full turn, so 0 is opposite the dosage indicator again. You’ve now set 20 units. Keep turning the cap until 6 is opposite the dosage indicator. On the push-button scale you’ll see a 20-line. Add the 6 from the dosage indicator to the 20 on the push-button scale. There, you’ve set 26 units (picture F).

To check a dose you set
- Note the figure on the cap next to the dosage indicator
- Note the highest figure you can see on the push-button scale
- Add the two together to show the dose you set
- If you have set a wrong dose, simply turn the cap forwards or backwards until you set the right number of units.

The maximum dose is 78 units
- Don’t try to set a dose higher than 78 units. Otherwise, insulin will leak out of the needle and the dose will be incorrect
- If you have, by mistake, tried to set a dose over 78 units, follow these steps:
  Turn the cap back as far as you can. Turn it till the push-button is fully down and you can feel resistance. Then take the cap off and put it back on again, lining up the 0 next to the dosage indicator. Now set the dose again. Remember that 78 units is the maximum dose
- After the dose is set, remove the cap to inject the insulin. Go straight on to section Injecting the insulin.

Injecting the insulin
- Insert the needle into your skin. Use the injection technique advised by your doctor
- Deliver the dose by pressing the push-button fully down. Be careful only to push the push-button when injecting
• Keep the push-button fully depressed after the injection until the needle has been withdrawn from the skin. The needle must remain under the skin for at least 6 seconds. This will ensure that the full dose has been delivered.

Subsequent injections
• Always check that the push-button is completely down. If not, turn the cap until the push-button is fully depressed, then proceed as described in Getting started
• You may hear a clicking sound when you press the push-button. Don’t use this to set or check your dose; it may not be accurate
• You can’t set a dose higher than the number of units left in the cartridge
• You can use the insulin level indicator to estimate how much is left, but you can’t use it to set or select your dose.

Removing the needle
• Replace the big outer needle cap and unscrew the needle. Dispose of it carefully.

Use a new needle for each injection.
Remove the needle after each injection and store NovoLet without a needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing.
Health care professionals, relatives and other carers must follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Close your Actrapid NovoLet fully with 0 next to the dosage indicator.
Dispose of your used Actrapid NovoLet carefully without the needle attached.

Maintenance

Your Actrapid NovoLet is designed to work accurately and safely. It must be handled with care.
Do not refill Actrapid NovoLet.
You can clean the exterior of your Actrapid NovoLet by wiping it with a medicinal swab. Do not soak it, wash or lubricate it. This may damage the mechanism.
Read all of this leaflet carefully before you start using your insulin.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, diabetes nurse or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or your pharmacist.

This side of the leaflet:
1. What Actrapid is and what it is used for
2. Before you use Actrapid
3. How to use Actrapid
4. What to do in an emergency
5. Possible side effects
6. How to store Actrapid
7. Further information

Overleaf: How to use your InnoLet

1. WHAT ACTRAPID IS AND WHAT IT IS USED FOR

Actrapid is human insulin to treat diabetes. Actrapid is a fast-acting insulin. This means that it will start to lower your blood sugar about half an hour after you take it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with longer-acting insulin products.

2. BEFORE YOU USE ACTRAPID

Do not use Actrapid

► If you are allergic (hypersensitive) to this insulin product, metacresol or any of the other ingredients (see 7 Further information). Look out for the signs of allergy in 5 Possible side effects
► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 What to do in an emergency for more about hypos.

Take special care with Actrapid

► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
► If you are drinking alcohol: watch for signs of a hypo and never drink alcohol on an empty stomach
► If you are exercising more than usual or if you want to change your usual diet
► If you are ill: carry on taking your insulin
► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections.

Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

Pioglitazone (oral antidiabetic medicine used for the treatment of type 2 diabetes mellitus)
Since some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Pregnancy and breast-feeding

If you are pregnant, planning a pregnancy or breast-feeding: please contact your doctor for advice.

Driving and using machines

If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

3. HOW TO USE ACTRAPID

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.

If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection.

Injecting insulin

See overleaf for detailed instructions.

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.

Do not use Actrapid

► In insulin infusion pumps
► If InnoLet is dropped, damaged or crushed there is a risk of leakage of insulin
► If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
► If it does not appear water clear and colourless.

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.

4. WHAT TO DO IN AN EMERGENCY
If you get a hypo

A hypo means your blood sugar level is too low. The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you get any of these signs, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don't take any insulin if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death.

If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon

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

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycaemia). The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

If you get any of these signs, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

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

5. POSSIBLE SIDE EFFECTS
Like all medicines, Actrapid can cause side effects, although not everybody gets them. Actrapid may cause hypoglycaemia (low blood sugar). See the advice in 4 What to do in an emergency.

**Side effects reported uncommonly** (in less than 1 patient in 100)

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

**Changes at the injection site (Lipodystrophy).** If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or diabetes nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

**Signs of allergy.** Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

**Seek medical advice immediately:**
- if signs of allergy spread to other parts of the body, or
- if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

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

**Painful neuropathy** (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

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

**Side effects reported very rarely** (in less than 1 patient in 10,000)

**Diabetic retinopathy** (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or pharmacist.

6. **HOW TO STORE ACTRAPID**

Keep out of the reach and sight of children.

Do not use Actrapid after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

**The InnoLet that is not being used** is to be stored in a refrigerator (2°C - 8°C). Do not store them in or too near the freezer section or cooling element. Do not freeze.

**The InnoLet that is being used,** about to be used or carried as a spare is not to be kept in a refrigerator. You can carry it with you and keep it at room temperature (not above 30ºC) for up to 6 weeks. Always keep the pen cap on your InnoLet when you’re not using it in order to protect it from light. Actrapid must be protected from excessive heat and sunlight.
Actrapid should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

What Actrapid contains

- **The active substance** is insulin human made by recombinant biotechnology. 1 ml contains 100 IU of insulin human. 1 pre-filled pen contains 3 ml equivalent to 300 IU

- **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

The solution for injection comes as a clear, colourless, aqueous solution. It is supplied in packs of 1, 5 or 10 pre-filled pens of 3 ml. Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer

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

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

This leaflet was last approved in
Information on how to use Actrapid InnoLet

Please read the following instructions carefully before using your Actrapid InnoLet.

Introduction

Actrapid InnoLet is a simple, compact pre-filled pen able to deliver 1 to 50 units in increments of 1 unit. InnoLet is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. Be sure you are not using any counterfeit needles. Ask your pharmacist. As a precautionary measure, always carry a spare insulin delivery device in case your InnoLet is lost or damaged.

Preparing for injection

Check the label to make sure that your Actrapid InnoLet contains the correct type of insulin. Take off the pen cap (as shown by the arrow).

Attaching the needle

• Disinfect the rubber membrane with a medicinal swab
• Always use a new needle for each injection to prevent contamination
• Remove the protective tab from a new disposable needle
• Screw the needle straight and tightly onto Actrapid InnoLet (picture 1A)
• Pull off the big outer needle cap and the inner needle cap. You may want to store the big outer needle cap in the compartment.
Priming to expel air

Small amounts of air may collect in the needle and cartridge during normal use. To avoid injection of air and ensure proper dosing:

- **Dial 2 units** by turning the dose selector clockwise
- **Hold Actrapid InnoLet 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 (picture 1B)
- **Keeping the needle upwards, press the push-button** and the dose selector returns to zero
- **A drop of insulin must 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 device is defective and must not be used.

Setting the dose

- **Always check that the push-button is fully depressed and the dose selector is set at zero**
- **Dial the number of units required** by turning the dose selector clockwise (picture 2). Do not use the residual scale to measure your dose of insulin
- **You will hear a click for every single unit dialled.** The dose can be corrected by turning the dial either way.

You cannot set a dose larger than the number of units left in the cartridge.
Injecting the insulin

- **Insert the needle into your skin.** Use the injection technique advised by your doctor
- **Deliver the dose by pressing the push-button fully down** (picture 3). You will hear clicks as the dose selector returns to zero
- **After the injection, the needle must remain under the skin for at least 6 seconds** to ensure that the full dose has been delivered
- **Make sure not to block the dose selector while injecting,** as the dose selector must be allowed to return to zero when you press the push-button
- **Remove the needle after each injection.**

Removing the needle

- **Replace the big outer needle cap and unscrew the needle** (picture 4). Dispose of it carefully.

Use a new needle for each injection. Remove the needle after each injection and store InnoLet without a needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing. Health care professionals, relatives and other carers must follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration. Dispose of your used Actrapid InnoLet carefully without the needle attached.
Maintenance

Your Actrapid InnoLet is designed to work accurately and safely. It must be handled with care. Do not refill Actrapid InnoLet. You can clean your Actrapid InnoLet by wiping it with a medicinal swab. Do not soak it, wash or lubricate it. This may damage the mechanism.
Actrapid is human insulin to treat diabetes. Actrapid is a fast-acting insulin. This means that it will start to lower your blood sugar about half an hour after you take it, and the effect will last for approximately 8 hours. Actrapid is often given in combination with longer-acting insulin products.

2. BEFORE YOU USE ACTRAPID

Do not use Actrapid

► If you are allergic (hypersensitive) to this insulin product, metacresol or any of the other ingredients (see 7 Further information). Look out for the signs of allergy in 5 Possible side effects

► If you feel a hypo coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 What to do in an emergency for more about hypos.

Take special care with Actrapid

► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands

► If you are drinking alcohol: watch for signs of a hypo and never drink alcohol on an empty stomach

► If you are exercising more than usual or if you want to change your usual diet

► If you are ill: carry on taking your insulin

► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of your injections.

Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed.
Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

Pioglitazone (oral antidiabetic medicine used for the treatment of type 2 diabetes mellitus)
Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Pregnancy and breast-feeding

If you are pregnant, planning a pregnancy or breast-feeding: please contact your doctor for advice.

Driving and using machines

If you drive or use tools or machines: watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

3. HOW TO USE ACTRAPID

Talk about your insulin needs with your doctor and nurse. Follow their advice carefully. This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.
Eat a meal or snack containing carbohydrates within 30 minutes of the injection.
It is recommended that you measure your blood glucose regularly.

Injecting insulin

See overleaf for detailed instructions.

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.

Do not use Actrapid

► In insulin infusion pumps
► If FlexPen is dropped, damaged or crushed there is a risk of leakage of insulin
► If it hasn’t been stored correctly or been frozen (see 6 How to store Actrapid)
► If it does not appear water clear and colourless.

Actrapid is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 Possible side effects). 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. Your insulin will work more quickly if you inject it around the waist.

4. WHAT TO DO IN AN EMERGENCY
If you get a hypo

A hypo means your blood sugar level is too low. **The warning signs of a hypo** may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

**If you get any of these signs**, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. **Don't take any insulin** if you feel a hypo coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

► **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
► **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Using glucagon

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

Causes of a hypo

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

**If your blood sugar gets too high**

Your blood sugar may get too high (this is called hyperglycaemia). **The warning signs** appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.

**If you get any of these signs**, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away. These may be signs of a very serious condition called diabetic ketoacidosis. If you don’t treat it, this could lead to diabetic coma and death.

Causes of hyperglycaemia

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

5. **POSSIBLE SIDE EFFECTS**
Like all medicines, Actrapid can cause side effects, although not everybody gets them. Actrapid may cause hypoglycaemia (low blood sugar). See the advice in 4 What to do in an emergency.

**Side effects reported uncommonly** (in less than 1 patient in 100)

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

**Changes at the injection site (Lipodystrophy).** If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

**Signs of allergy.** Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

**Seek medical advice immediately:**
- if signs of allergy spread to other parts of the body, or
- if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

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

**Painful neuropathy** (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

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

**Side effects reported very rarely** (in less than 1 patient in 10,000)

**Diabetic retinopathy** (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

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6. **HOW TO STORE ACTRAPID**

Keep out of the reach and sight of children.

Do not use Actrapid after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

**The FlexPen that is not being used** is to be stored in a refrigerator (2°C - 8°C). Do not store them in or too near the freezer section or cooling element. Do not freeze.

**The FlexPen that is being used,** about to be used or carried as a spare is not to be kept in a refrigerator. You can carry it with you and keep it at room temperature (not above 30°C) for up to 6 weeks. Always keep the pen cap on your FlexPen when you’re not using it in order to protect it from light. Actrapid must be protected from excessive heat and sunlight.
Actrapid should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

What Actrapid contains

- The active substance is insulin human made by recombinant biotechnology. 1 ml contains 100 IU of insulin human. 1 pre-filled pen contains 3 ml equivalent to 300 IU

- 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
The solution for injection comes as a clear, colourless, aqueous solution.
It is supplied in packs of 1, 5 or 10 pre-filled pens of 3 ml. Not all packs may be marketed.

Marketing Authorisation 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 W5, S6, P5, K7, or ZF Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark is the manufacturer

- If the second and third characters are H7 or T6 Novo Nordisk Production SAS, 45 Avenue d’Orléans F-28002 Chartres, France is the manufacturer.

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

This leaflet was last approved in
Introduction

Please read the following instructions carefully before using your Actrapid FlexPen.

Your FlexPen is a unique dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. FlexPen is designed and tested 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.

The colour of the pen in the illustrations differs from your FlexPen.

Actrapid FlexPen

![Diagram of Actrapid FlexPen]

Maintenance

Your FlexPen is designed to work accurately and safely. It must be handled with care. If it is dropped or crushed, there is a risk of damage and leakage of insulin.

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.

Preparing your Actrapid FlexPen

Check the label to make sure that your FlexPen contains the correct type of insulin.

A
Pull off the pen cap.

Disinfect the rubber membrane with a medicinal swab.
B
Remove the protective 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.

• Always use a new needle for each injection to prevent contamination.
• Be careful not to bend or damage the needle before use.
• To reduce the risk of unexpected needle sticks, never put the inner needle cap back on when you have removed it from the needle.

Checking the insulin flow

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:

E
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 six times.

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

Selecting your dose

Check that the dose selector is set at 0.

H
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.
• Do not use the residual scale to measure your dose of insulin.

Making the injection

Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.

I
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 after the injection until the needle has been withdrawn from the skin.

The needle must remain under the skin for at least six seconds. This will ensure that the full dose has been injected.

K
Lead the needle into the big outer needle cap without touching the big outer needle cap. 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 otherwise the liquid may leak out which can cause inaccurate dosing.

• Caregivers should be most careful when handling used needles to avoid needle sticks.

• Dispose of the used FlexPen carefully without the needle attached.

• Do not share your FlexPen with anyone else.