

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Insulatard FlexPen 100 IU/ml
Suspension for injection in a pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Insulatard FlexPen is a suspension of isophane (NPH) insulin.

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

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection
Insulatard FlexPen is a cloudy, white, aqueous suspension of insulin human.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of diabetes mellitus.

4.2 Posology and method of administration

Dosage is individual and determined by the physician in accordance with the needs of the patient.

The average range of total daily insulin requirement for maintenance therapy in type 1 diabetic patients lies between 0.5 and 1.0 IU/kg. However, in pre-pubertal children it usually varies from 0.7 to 1.0 IU/kg, but can be much lower during the period of partial remission. In insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher.

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

In patients with diabetes mellitus optimised metabolic control effectively delays the onset and slows the progression of late diabetic complications. Optimised metabolic control, including glucose monitoring, is therefore recommended.

In the elderly the primary aim of treatment may be symptom relief and avoidance of hypoglycaemic events.

Dosage adjustment

Insulatard is a suspension of isophane (NPH) insulin.

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

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 undertake increased physical activity or change their usual diet.

Administration

Insulatard is usually administered subcutaneously in the thigh. The abdominal wall, the gluteal region or the deltoid region may also be used. Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites. Injection into a lifted skin fold minimises the risk of intramuscular injection. Keep the needle under the skin for at least 6 seconds to make sure all of the dose is injected. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

Insulin suspensions are never to be administered intravenously.

Insulatard may also be used in combination with oral hypoglycaemic agents (OHA), when OHA alone has not given satisfactory control of blood glucose.

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

Insulatard FlexPen

FlexPen is a pre-filled pen designed to be used with NovoFine short cap needles (8 mm or shorter). The needle box is marked with an **S**.

FlexPen delivers 1-60 units in increments of 1 unit.

The pen is 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.

Insulin suspension should not be used if they do not appear uniformly white and cloudy after suspension.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to human insulin or any of the excipients.

4.4 Special warnings and precautions for use

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

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

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

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), species (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a change in dosage.

If an adjustment when switching the patients to Insulatard is needed, it may occur with the first dose or during the first several weeks or months.

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported

that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Patients whose blood glucose 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.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with the glucose metabolism. The physician must therefore take possible interactions into account.

The following substances may reduce insulin requirement:

Oral hypoglycaemic agents (OHA), octreotide, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, and anabolic steroids (except danazol and oxymetholone), quinine, quinidine and alpha-adrenergic blocking agents.

The following substances may increase insulin requirement:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and sympathomimetics, danazol, oxymetholone, growth hormone, diazoxide, asparaginase and nicotinic acid.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia. Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

4.6 Pregnancy and lactation

Pregnancy

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

If untreated during pregnancy, diabetes mellitus constitutes a risk in intrauterine development. Diabetes therapy must therefore be continued during pregnancy.

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

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

Lactation

There are no restrictions on the treatment of diabetes with Insulatard, during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the Insulatard dosage may need to be adjusted.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

The most often seen undesirable effect in insulin-treated patients is change in blood glucose levels. From clinical investigations it is known that major hypoglycaemia, defined as need for assistance in treatment, is occurring in approximately 20% of well-controlled patients. Based on post-marketing experience Adverse Drug Reactions including hypoglycaemia are rare (< 1/1,000). The below listings are all based on post-marketing experience.

Metabolism and nutrition disorders

Rare
(>1/10,000<1/1,000)
Change in blood glucose

Hypoglycaemia:
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Hyperglycaemia:
Usually the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.
In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis which is potentially lethal.
For precautions see section 4.4.

Eye disorders

Very rare
(<1/10,000)

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

General disorders and administration site conditions

Very rare
(<1/10,000)

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Very rare
(<1/10,000)

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

Very rare
(<1/10,000)

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

Very rare
(<1/10,000)

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

4.9 Overdose

Insulins have no specific overdose definitions. However, hypoglycaemia may develop over sequential stages:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carry some sugar lumps or e.g. a few biscuits.
- 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 trained person or glucose given intravenously by a medical professional. Glucose must also be given i.v, 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

Pharmacotherapeutic group: antidiabetic agent.

ATC code A10AC01.

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. Insulatard is classified as a long acting insulin.

Onset of action for Insulatard is within 1½ hours, reaches a maximum effect within 4-12 hours and the entire time of duration is up to 24 hours.

This profile is similar in children and adolescents.

5.2 Pharmacokinetic properties

In general, the pharmacokinetics of insulins are affected by significant intra- and interindividual variation.

Absorption

The maximum plasma concentration of the long acting insulin is reached within 4-12 hours after s.c. 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 s.c. tissue. The terminal half-life ($t_{1/2}$) is therefore a measure of the terminal 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 5-10 hours.

The pharmacokinetic profile is expected to be similar in children and adolescents compared to adults.

5.3 Preclinical safety data

Pre-clinical tests in various species have been performed and none of these resulted in unexpected, remarkable findings.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Disodium phosphate dihydrate
Metacresol
Phenol
Zinc chloride
Protamine sulphate
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2 Incompatibilities

In general terms, insulin should only be added to compounds with which it has known compatibility. Insulin suspensions should not be added to infusion fluids.

6.3 Shelf Life

30 months.

After first use Insulatard FlexPen may be used or carried as a spare for 4 weeks.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator) not near a freezing compartment.

Do not freeze.

Insulin preparations, which have been frozen, must not be used.

Keep the container in the outer carton in order to protect insulin from light.

After first opening: do not store above 37°C.

6.5 Nature and contents of container

Pre-filled pen (multidose disposable) comprising an injector with a cartridge (3 ml). The cartridge is made of glass (type 1) and the cartridge is closed with a brombutyl laminate rubber stopper, and a stopper shaped as a plunger. The cartridge contains a glass ball to facilitate the resuspension.

The pre-filled pens are packed in carton.

The 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
2880 Bagsværd
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 218/26/7

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2002

Date of last renewal: 01 February 2004

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March 2005