Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Insulatard InnoLet 100 IU/ml
Suspension 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.

Insulatard is a suspension of isophane (NPH) insulin.

For excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled pen.

Insulatard is a cloudy, white, aqueous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of diabetes mellitus.

4.2 Posology and method of adminstration

Insulatard is a long-acting insulin.

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

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

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

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

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

Renal or hepatic impairment may reduce insulin requirement.

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

Administration
For subcutaneous use.

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

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

Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.
Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.

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

Insulin suspensions are never to be administered intravenously.

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

Insulatard InnoLet 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.**
InnoLet delivers 1-50 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.
Hypoglycaemia can generally be corrected by immediate carbohydrate intake. In order to be able to take action immediately, patients should carry glucose with them at all times.
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly (see section 4.8 Undesirable effects).

Usual warning symptoms may disappear in patients with longstanding diabetes.
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), species (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a change in dosage.
If an adjustment is needed when switching the patients to Insulatard, it may occur with the first dose or during the first several weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

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

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

Insulatard contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Octreotide/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 increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy values.

Insulin treatment of the nursing mother presents no risk to the baby. However, the 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 a change in blood glucose levels. **From clinical investigations it is known that major hypoglycaemia, defined as need for assistance in treatment, occurs in approximately 20% of well-controlled patients.** Based on post-marketing experience adverse drug reactions including hypoglycaemia have been reported rarely (>1/10,000 <1/1,000). The listings below are all based on post-marketing experience and is subject to underreporting and should be interpreted in that light.

Metabolism and nutrition disorders

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

Eye disorders

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

General disorders and administration site conditions

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

	palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life threatening.
Very rare (<1/10,000)	Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

4.9 Overdose

A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages:
▪ Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice
▪ Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Insulatard is a long-acting insulin.
Onset of action is within 1½ hours, reaches a maximum effect within 4-12 hours and the entire time of duration is approximately 24 hours.

5.2 Pharmacokinetic properties

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

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

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

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

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

Elimination
The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{½}$) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ of about 5-10 hours.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride
Glycerol
Metacresol
Phenol
Disodium phosphate dihydrate
Sodium hydroxide or/and hydrochloric acid (for pH adjustment)
Protamine sulphate
Water for injections

6.2 Incompatibilities

Insulin suspensions should not be added to infusion fluids.
Medicinal products added to the insulin suspension may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.

6.3 Shelf Life

30 months.

After first opening: 6 weeks.

6.4 Special precautions for storage

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

During use: do not refrigerate. Do not store above 30°C.
Keep the pen cap on in order to protect the insulin 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 cartridge contains a glass ball to facilitate the re-suspension. 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

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

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 218/26/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 2000.

Date of last renewal: 1 February 2004.

10 DATE OF REVISION OF THE TEXT

March 2005.