SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Insulatard 40 international units/ml suspension for injection in vial.
Insulatard 100 international units/ml suspension for injection in vial.
Insulatard Penfill 100 international units/ml suspension for injection in cartridge.
Insulatard InnoLet 100 international units/ml suspension for injection in pre-filled pen.
Insulatard FlexPen 100 international units/ml suspension for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulatard vial (40 international units/ml)
1 vial contains 10 ml equivalent to 400 international units. 1 ml suspension contains 40 international units isophane (NPH) insulin human* (equivalent to 1.4 mg).

Insulatard vial (100 international units/ml)
1 vial contains 10 ml equivalent to 1,000 international units. 1 ml suspension contains 100 international units isophane (NPH) insulin human* (equivalent to 3.5 mg).

Insulatard Penfill
1 cartridge contains 3 ml equivalent to 300 international units. 1 ml suspension contains 100 international units isophane (NPH) insulin human* (equivalent to 3.5 mg).

Insulatard InnoLet/Insulatard FlexPen
1 pre-filled pen contains 3 ml equivalent to 300 international units. 1 ml suspension contains 100 international units isophane (NPH) insulin human* (equivalent to 3.5 mg).

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

Excipient with known effect:

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Insulatard is indicated for treatment of diabetes mellitus.

4.2 Posology and method of administration

Posology

The potency of human insulin is expressed in international units.

Insulatard dosing is individual and determined in accordance with the needs of the patient. 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. Blood glucose monitoring is recommended to achieve optimal glycaemic control.

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

Special populations

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

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

Paediatric population
Insulatard can be used in children and adolescents.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products, adjustment of the Insulatard dose and timing of administration may be necessary.

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

Method of administration

Insulatard is a human insulin with gradual onset and long duration of action.

Insulatard is administered subcutaneously by injection in the thigh, the abdominal wall, the gluteal region or the deltoid region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8). Insulin suspensions are never to be administered intravenously. Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.

The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected. Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

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

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

Insulatard vial (40 international units/ml)/Insulatard vial (100 international units/ml)
Administration with a syringe
Insulatard vials are for use with insulin syringes with a corresponding unit scale.

Insulatard Penfill

Administration with an insulin delivery system

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

Insulatard InnoLet

Administration with InnoLet

Insulatard 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. Insulatard InnoLet is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

Insulatard FlexPen

Administration with FlexPen

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Hyperglycaemia

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

Hypoglycaemia

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

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

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

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

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

Transfer from other insulin medicinal products

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

Injection site reactions

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

Skin and subcutaneous tissue disorders

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

Combination of Insulatard 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 Insulatard is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Avoidance of accidental mix-ups/medication errors

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

Traceability

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

The following substances may increase the patient's insulin requirement:

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

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Summary of the safety profile

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

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

diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

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

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

Description of selected adverse reactions

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

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

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

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Paediatric population

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

Other special populations

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

Reporting of suspected adverse reactions

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

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting
Website:
www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate-acting, insulin (human). ATC code: A10AC01.

Mechanism of action and pharmacodynamic effects

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

Insulatard is a human insulin with gradual onset and long duration of action.
Onset of action is within 1½ hours, reaches a maximum effect within 4–12 hours and the entire duration of action 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 dose, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin medicinal products are therefore affected by significant intra- and inter-individual variation.

Absorption

The maximum plasma concentration 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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc chloride
Glycerol
Metacresol
Phenol
Disodium phosphate dihydrate
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)
Protamine sulfate
Water for injections

6.2 Incompatibilities

Insulin medicinal products should only be added to compounds with which it is known to be compatible. Insulin suspensions should not be added to infusion fluids.

6.3 Shelf life

Before opening: 30 months.

Insulatard vial (40 international units/ml)

During use or when carried as a spare: The product can be stored for a maximum of 4 weeks. Store below 25°C.

Insulatard vial (100 international units/ml)

During use or when carried as a spare: The product can be stored for a maximum of 6 weeks. Store below 25°C.

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

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C – 8°C). Do not freeze.

Insulatard vial (40 international units/ml)/Insulatard vial (100 international units/ml)
During use or when carried as a spare: Store below 25°C. Do not refrigerate or freeze.
Keep the vial in the outer carton in order to protect from light.

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

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

6.5 Nature and contents of container

Insulatard vial (40 international units/ml)/Insulatard vial (100 international units/ml)
Vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of suspension.

Pack sizes of 1 and 5 vials of 10 ml or a multipack of 5 packs of 1 x 10 ml vial. Not all pack sizes may be marketed.

Insulatard Penfill
Cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension. The cartridge contains a glass ball to facilitate resuspension.

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

Insulatard InnoLet/Insulatard FlexPen
Cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension in a pre-filled multidose disposable pen made of polypropylene. The cartridge contains a glass ball to facilitate resuspension.

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

6.6 Special precautions for disposal and other handling

After removing Insulatard vial, cartridge or pre-filled pen from the refrigerator, it is recommended to allow the Insulatard vial, cartridge or pre-filled pen to reach room temperature before resuspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the resuspended liquid is not uniformly white and cloudy.

Insulatard which has been frozen must not be used.

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

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

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

The cartridge must not be refilled.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

Insulatard vial (40 international units/ml)
EU/1/02/233/001
EU/1/02/233/002
EU/1/02/233/016

Insulatard vial (100 international units/ml)
EU/1/02/233/003
EU/1/02/233/004
EU/1/02/233/017

Insulatard Penfill
EU/1/02/233/005
EU/1/02/233/006
EU/1/02/233/007

Insulatard InnoLet

EU/1/02/233/010
EU/1/02/233/011
EU/1/02/233/012

Insulatard FlexPen
EU/1/02/233/013
EU/1/02/233/014
EU/1/02/233/015

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

09/2020

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