SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Insulatard Flexpen

2. Qualitative and quantitative composition

Each ml contains: 100 IU corresponds to 0.035 mg of anhydrous human insulin produced by recombinant DNA technology in Saccharomyces cerevisiae.

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

Insulatard is a mixture of dissolved insulin and isophane (NPH) insulin.

Insulatard consists of 30% dissolved insulin and 70% isophane insulin.

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. 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. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. 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.

Administration with FlexPen

Insulatard is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. it delivers 1-50 units in increments of 1 unit. Insulatard 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.

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.

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*
General disorders and administration site conditions	Uncommon – Injection site reactions
	Uncommon – Oedema

* see Description of selected adverse reactions

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.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area reduces the risk of developing these reactions.

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 authorization of the medical products 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 TMDA ADR reporting tool; website: *https://imis.tmda.go.tz/arrt* or search for TMDA adverse reactions reporting tool in the google play store.

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
Meta-cresol
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.

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.

During use or when carried as a spare: Store below 30°C. Do not refrigerate or freeze.

Keep the pen cap on in order to protect from light.

6.5 Nature and contents of container

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene in a carton. The cartridge contains a glass ball to facilitate the resuspension.

Pack sizes of 1 x 3ml pre-filled pen.

6.6 Special precautions for disposal and other handling
6.5 Nature and contents of container

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene in a carton. The cartridge contains a glass ball to facilitate the resuspension.

Pack sizes of 1 x 3ml pre-filled pen.

6.6 Special precautions for disposal and other handling

Pens should only be used in combination with products that are compatible with them and allow the pen to function safely and effectively. Needles and Mixtard® FlexPen® must not be shared.

The container must not be refilled. Insulin preparations which have been frozen must not be used.

After removing Insulatard from the refrigerator, it is recommended to allow the pen to reach room temperature before re-suspending the insulin as instructed for first time use.

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

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

7. Marketing authorization holder and manufacturing site

7.1 Marketing authorization holder

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

7.2 manufacturing site

Novo Nordisk
Novo Alle Dk-2880, Post Box 2000
Bagsvaerd
Denmark

8. Registration number

TZ 17 H 0231

9. Date of first registration

11/9/2017

10. Date of revision of the text

June 2020