

Regulatory Operations

Insert: 2010-125x295-001  
Current 1.0

110 vial Professional

Colour: PMS 280C

100 IU/ml

**Insulatard®**

Suspension for injection in vial.

**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 1,000 IU.  
One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.  
Insulatard® is a suspension of isophane (NPH) insulin.

**Pharmaceutical form**

Suspension for injection in vial.  
Cloudy, white, aqueous suspension.

**Therapeutic indications**

Treatment of diabetes mellitus.

**Posology and method of administration**

Insulatard® is a long-acting insulin and may be used alone or in combination with fast or rapid-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.

**Dosage adjustment**

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. 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.

**Administration**

For subcutaneous use. Insulin suspensions are never to be administered intravenously.  
Insulatard® is 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. 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.  
Insulatard® vials are for use with insulin syringes with a corresponding unit scale.  
Insulatard® is accompanied by a package leaflet with detailed instructions for use to be followed.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

**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.

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, origin (human insulin, insulin analogue) and/or method of manufacture may result in a need for a change in dosage. Patients transferred to Insulatard® from another type of insulin may require an increased number of daily injections or change in dosage from that used with their usual insulin products. If an adjustment is needed when switching the patient to Insulatard®, it may occur with the first dose or during the first few weeks or months.

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 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 Insulatard®.

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.

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

**Combination of thiazolidinediones and insulin medicinal products**

Cases of congestive heart failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of congestive heart failure. This should be kept in mind if treatment with the combination of thiazolidinediones and insulin medicinal products is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac symptoms occurs.

**Interaction with other medicinal products and other forms of interaction**

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

**The following substances may reduce the patient's insulin requirement:**

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

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

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

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia. Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

**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 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.

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® dosage, diet or both may need to be adjusted.

**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.


**Undesirable effects****a. Summary of the safety profile**

The most frequently reported adverse reaction during treatment is hypoglycaemia. In clinical trials and during marketed use, the frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see section c 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 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.

**b. Tabulated list of adverse reactions**

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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

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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 section c

**c. Description of selected adverse reactions****Anaphylactic reactions**

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness) 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 concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

**Lipodystrophy**

Lipodystrophy is reported as uncommon. Lipodystrophy may occur at the injection site.

**Overdose**

A specific overdose of insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are 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 an oral carbohydrate is recommended for the patient in order to prevent a relapse.

**Pharmacodynamic properties**

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

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.

**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 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 ( $t_{1/2}$ ) 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 5 - 10 hours.

**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.

**List of excipients**

Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide/hydrochloric acid (for pH adjustment), protamine sulphate and water for injections.

**Incompatibilities**

Insulin suspensions should not be added to infusion fluids.

**Special precautions for storage**

Store in a refrigerator (2°C - 8°C). Keep away from the cooling element. Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Insulatard® must be protected from excessive heat and light.

After first opening or carried as a spare: Do not refrigerate.

The in-use shelf life is 6 weeks when stored below 25°C or 4 weeks when stored below 30°C.

**Nature and contents of container**

10 ml suspension in vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene) rubber and a protective tamper-proof plastic cap in a carton.

Pack sizes of 1 and 5 vials.

Not all pack sizes may be marketed.

**Special precautions for disposal and other handling**

Insulin preparations which have been frozen must not be used.

After removing Insulatard® vial from the refrigerator, it is recommended to allow the vial to reach room temperature before resuspending 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.

**Produced by**

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

**Insulatard® suspension for injection in vial.****INSTRUCTIONS FOR USE FOR THE PATIENT****Do not use Insulatard®**

- ▶ **In insulin infusion pumps.**
- ▶ **If you are allergic (hypersensitive)** to human insulin or any of the other ingredients in Insulatard®.
- ▶ **If you suspect hypoglycaemia** (low blood sugar) is starting.
- ▶ **If the protective cap is loose or missing.** Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your pharmacy.
- ▶ **If it has not been stored correctly** or been frozen.
- ▶ **If the resuspended insulin does not appear uniformly white and cloudy.**

**Before using Insulatard®**

- ▶ **Check the label to make sure** it is the right type of insulin.
- ▶ **Remove the protective cap.**

**How to use this insulin**

**Insulatard® is administered by injection under the skin** (subcutaneously). Never inject your insulin directly into a vein or muscle. Always vary the sites you inject within the same region, to reduce the risk of developing lumps or skin pitting. The best places to give yourself an injection are: your buttocks; the front of your thighs or upper arms.

**How to inject Insulatard® on its own or to mix with fast-acting insulin**

- ▶ **Make sure you have the correct syringe** with the corresponding unit scale for insulin injections.
- ▶ **Draw air into the syringe** in the same amount as the dose of insulin you need.
- ▶ **Follow the instructions** given by your doctor or nurse.
- ▶ **Just before injecting this insulin**, roll the vial between your hands until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.
- ▶ **Inject the insulin** under the skin. Use the injection technique advised by your doctor or nurse.
- ▶ **Keep the needle under your skin** for at least 6 seconds to make sure that the full dose has been delivered.

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