

Insulatard®

FlexPen®

100 IU/ml

Suspension for injection in pre-filled pen.

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.

Pharmaceutical form

Suspension for injection in pre-filled pen.

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 by injection in the thigh. If convenient, the abdominal wall, the gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.

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.

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 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.

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 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.

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.

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).

Immune system disorders	Uncommon – Urticaria, rash
	Very rare – Anaphylactic reactions*
Metabolism and nutrition	Very common – Hypoglycaemia*

disorders	
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 section c

† ADR from postmarketing sources

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.

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.

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.

If there are 6 months or more until the expiry date, the product may be stored outside of the refrigerator (below 30°C) for a maximum of 4 weeks before it is taken into use or carried as a spare. After storage outside of the refrigerator, the product must not be returned to the refrigerator. Please record the beginning of storage outside of the refrigerator on the product carton.

Keep the pen cap on FlexPen® 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 30°C.

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

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 Insulatard® FlexPen® must not be shared. The container must not be refilled.

Insulin preparations which have been frozen must not be used.

After removing Insulatard® FlexPen® from the refrigerator, it is recommended to allow FlexPen® 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. The patient should be advised to discard the needle after each injection.

Manufactured by:

Novo Nordisk Production SAS, 45 Avenue d'Orléans, F-28000 Chartres, France

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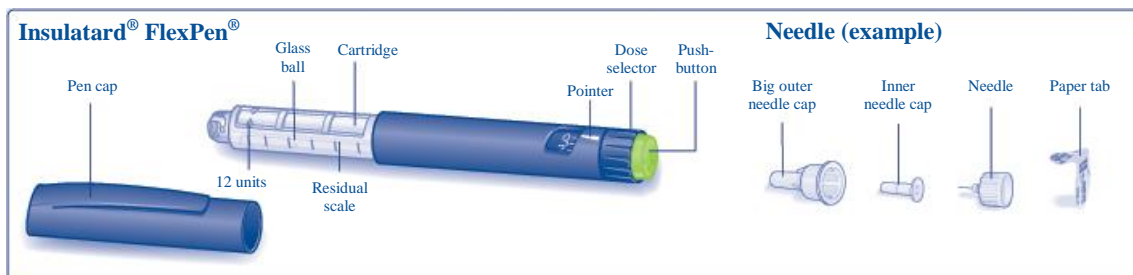
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Instructions on how to use Insulatard® suspension for injection in FlexPen®

Read the following instructions carefully before using your FlexPen®. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Your FlexPen® is a pre-filled dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. FlexPen® is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm. As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen® is lost or damaged.



Caring for your pen

Your FlexPen® must be handled with care. If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

You can clean the exterior of your FlexPen® by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your FlexPen®. Once empty, it must be disposed of.

Preparing your Insulatard® FlexPen®

A

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin.

This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Every time you use a new pen

Let the insulin reach room temperature before you use it. This makes it easier to resuspend. Pull off the pen cap (see A).



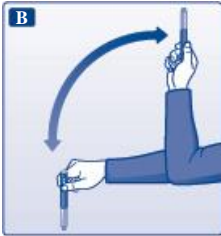
B

Before your first injection with a new pen, you must resuspend the insulin:

Move the pen up and down twenty times between the two positions as shown, so the glass ball moves from one end of the cartridge to the other. Repeat until the liquid appears uniformly white and cloudy.

For every following injection, move the pen up and down between the two positions at least 10 times until the liquid appears uniformly white and cloudy.

Always make sure that you have resuspended the insulin prior to each injection. This reduces the risk of too high or too low blood sugar level. After you have resuspended the insulin, complete all the following steps of injection without delay.



⚠ Always check there are at least 12 units of insulin left in the cartridge to allow resuspension. If there are less than 12 units left, use a new pen. 12 units are marked on the residual scale. See the big picture on top of this instruction.

⚠ Do not use the pen if the **resuspended** insulin does not look **uniformly white and cloudy**.

Attaching a needle

C

Remove the paper tab from a new disposable needle.

Screw the needle straight and tightly onto your FlexPen®.



D

Pull off the big outer needle cap and keep it for later.



E

Pull off the inner needle cap and dispose of it.

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



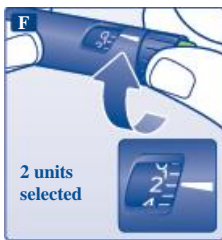
- ⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- ⚠ Be careful not to bend or damage the needle before use.

Checking the insulin flow

F

Prior to each injection, small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:

Turn the dose selector to select 2 units.



G

Hold your FlexPen® with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.



H

Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If a drop of insulin still does not appear, the pen is defective, and you must use a new one.



- ⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.
- ⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Selecting your dose

I

Check that the dose selector is set at 0.

Turn the dose selector to select the number of units you need to inject.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.



- △ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
- △ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Making the injection

J

Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.

Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.

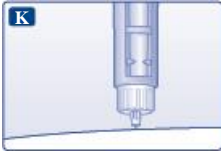


K

Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose.

Withdraw the needle from the skin, then release the pressure on the push-button.

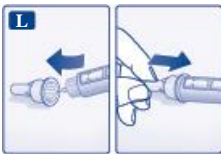
Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



L

Lead the needle into the big outer needle cap without touching it. When the needle is covered, carefully push the big outer needle cap completely on and then unscrew the needle.

Dispose of it carefully and put the pen cap back on.



- ⚠ Always remove the needle after each injection and store your FlexPen® without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Further important information

- ⚠ Caregivers must be very careful when handling used needles – to reduce the risk of needle sticks and cross-infection.
- ⚠ Dispose of your used FlexPen® carefully without the needle attached.
- ⚠ Never share your pen or your needles with other people. It might lead to cross-infection.
- ⚠ Never share your pen with other people. Your medicine might be harmful to their health.
- ⚠ Always keep your pen and needles out of sight and reach of others, especially children.