Suspension for injection in a cartridge

**Qualitative and quantitative composition**
Insulin human, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).
1 ml contains 100 IU of insulin human.
1 cartridge 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 a cartridge
Insulatard is a cloudy, white, aqueous suspension.

**Clinical particulars**
**Therapeutic indications**
Treatment of diabetes mellitus.

**Posology and method of administration**
Insulatard is a long-acting insulin.

**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.

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 of late diabetic complications. Close blood glucose monitoring is therefore recommended.

**Dosage adjustment**
Concomitant illness, especially infections and febrile 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.

**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.
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.
The cartridges are designed to be used with Novo Nordisk delivery systems (durable devices for repeated use) and NovoFine® needles. Detailed instruction accompanying the delivery system must be followed.

**Contraindications**
Hypersensitivity to the active substance or to any of the excipients.
Hypoglycaemia.

**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 and 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 (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for 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.

As with any insulin therapy, injection site reactions may occur and include pain, itching, hives, swelling and inflammation.

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.

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 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.

Insulatard contains metacresol, which may cause allergic reactions.

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

A number of medicinal products are known to interact with glucose metabolism. The physician must therefore take possible interactions into account and should always ask his 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, alcohol, anabolic steroids and sulphonamides.

The following substances may increase insulin requirement:

- Oral contraceptives, 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.

**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 subsequently increase during the second and third trimesters. After delivery, insulin requirements return rapidly to prepregnancy values. 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 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.

**Undesirable effects**
As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to Insulatard are listed below. The frequencies are defined as: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000, including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Immune system disorders**
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
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.

**Nervous system disorders**
Very rare - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

**Eye disorders**
Very rare - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy.
These symptoms are usually of transitory nature.

**Skin and subcutaneous tissue disorders**
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

**General disorders and administration site conditions**
Uncommon - Injection site reactions
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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 (t½) 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 t½ of a few minutes). Trials have indicated a t½ of about 5 - 10 hours.

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

Pharmaceutical particulars
List of excipients
- Zinc chloride
- Glycerol
- Metacresol
- Phenol
- Disodium phosphate dihydrate
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)
- Protamine sulphate
- Water for injections

Incompatibilities
In general terms, insulin products should only be added to compounds with which it is known to be compatible. Insulin suspensions should not be added to infusion fluids.

Shelf life
30 months when stored between 2°C - 8°C.
Insulatard Penfill can be used or carried as a spare (below 30°C) for 6 weeks.
Store in a refrigerator (2°C - 8°C) not in or too near the freezer section or cooling element.
Do not freeze.
During use: do not refrigerate. Do not store above 30°C.
After removing Insulatard Penfill from the refrigerator it is recommended to allow the Penfill to reach room temperature before resuspending the insulin as instructed for first time use.
Keep the cartridge in the outer carton in order to protect the insulin from light.
Protect from excessive heat and sunlight.

Nature and contents of container
Glass cartridge (type 1) with a bromobutyl rubber plunger and a bromobutyl/polyisoprene rubber stopper. The cartridge contains a glass ball to facilitate the resuspension.
Pack sizes: 1, 5 and 10 cartridges x 3 ml.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
Cartridges should only be used in combination with products that are compatible with them and allow the cartridge to function safely and effectively.
Insulatard Penfill 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 resuspension.
Any unused product or waste material should be disposed of in accordance with local requirements.

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

Instructions to be given to the patient on how to handle
Insulatard® Penfill® Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine® needles.
If the patient is treated with Insulatard Penfill and another insulin Penfill cartridge, two insulin delivery systems should be used, one for each type of insulin.
Insulatard Penfill is for single person use only.
Do not refill Insulatard Penfill.

Before using Insulatard®
• Check the label to make sure it is the right type of insulin
• Always check the cartridge, including the rubber plunger (stopper). Do not use it if any damage is seen or if there is a gap between the rubber plunger and the white label band. See the diagram inside the cover of the delivery system manual for the names of the different parts of Penfill
• Disinfect the rubber membrane with a medicinal swab
• Always use a new needle for each injection to prevent contamination.

Do not use Insulatard®
• In insulin infusion pumps
• If the cartridge or the device containing the cartridge is dropped, damaged or crushed there is a risk of leakage of insulin
• If it has not been stored correctly or if it has been frozen
• If it’s not uniformly white and cloudy when it’s resuspended.

Resuspending the insulin
Resuspending is easier when the insulin has reached room temperature.
Before putting the Penfill cartridge into the insulin delivery system, move it up and down between positions A and B and back (see the picture) so that the glass ball moves from one end of the cartridge to the other at least 20 times. Repeat this movement at least 10 times before each injection. The movement must always be repeated until the liquid appears uniformly white and cloudy. Complete the other stages of injection without delay.
Check there are at least 12 units of insulin left in the cartridge to allow even resuspending. If there are less than 12 units left, use a new one.

**How to inject this insulin**

- Inject the insulin under the skin. Use the injection technique described in the delivery system manual
- Keep the needle under the skin for at least 6 seconds to make sure that the full dose has been delivered
- After each injection be sure to remove and discard the needle and store Insulatard without a needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing.

*Please go to www.novonordisk.com for more information.*