APPROVED PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

OPTISULIN® solution for injection

COMPOSITION

Each ml of the solution for injection contains 3,64 mg of the active ingredient insulin glargine, corresponding to 100 units (U) human insulin, 2,7 mg of the preservative metacresol, and 0,0626 mg of zinc chloride as stabiliser.
The 10 ml vial contains 0,02 mg polysorbate 20 as an additional stabiliser.

Each ml contains the following inactive ingredients: glycerol, hydrochloric acid, sodium hydroxide and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 21.1 Insulin preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Insulin glargine is a human insulin analogue produced by recombinant DNA technology using *Escherichia coli* (K12 strains). Insulin glargine is equipotent to human insulin.

In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. The time course of action of insulin glargine may be affected by physical activity and other variables.

In euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak, and the duration of its effect was prolonged.

The longer duration of action of insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.

Pharmacokinetic properties:

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the OPTISULIN injection solution (pH 4).

After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak.

Metabolism:

After subcutaneous injection of OPTISULIN in healthy subjects and diabetic patients, insulin glargine is rapidly metabolised at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of OPTISULIN. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with OPTISULIN is principally based on exposure to M1. Insulin glargine and the metabolite M2 were not detectable in the vast majority of subjects and, when they were detectable their concentration was independent of the administered dose of OPTISULIN.

INDICATIONS

For the treatment of adults, adolescents and children 6 years and older with diabetes mellitus, where treatment with insulin is required.

CONTRAINDICATIONS

OPTISULIN must not be used in:

- Patients hypersensitive to OPTISULIN or any of its excipients.
- Children < 6 years, as in this group efficacy and safety have not been demonstrated.

WARNINGS AND SPECIAL PRECAUTIONS

OPTISULIN should not be used for the treatment of diabetic ketoacidosis. Instead, intravenous regular insulin is recommended in such cases.

Hypoglycaemia:

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom sequelae of hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be made aware of circumstances where warning symptoms of hypoglycaemia are diminished.

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.
The prolonged effect of subcutaneous OPTISULIN may delay recovery from hypoglycaemia.

The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain conditions. These include patients:

- in whom glycaemic control is markedly improved
- in whom hypoglycaemia develops gradually
- who are elderly
- in whom an autonomic neuropathy is present
- with a long history of diabetes
- suffering from a psychiatric illness

- receiving concurrent treatment with certain other medicinal products (refer to "INTERACTIONS").

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Pens to be used with OPTISULIN cartridges:

The OPTISULIN cartridges should only be used with the following pen: Autopen 24. They should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pen.

Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. 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

symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

INTERACTIONS

A number of substances affect glucose metabolism and may require dose adjustment of OPTISULIN.

Substances that may increase the blood glucose lowering effect and increase susceptibility to hypoglycaemia include: oral antidiabetic agents; ACE inhibitors; disopyramide; fibrates; fluoxetine; MAO inhibitors; pentoxifylline; propoxyphene; salicylates and sulfonamide antibiotics.

Substances that may reduce the blood glucose lowering effect include: corticosteroids; danazol; diazoxide; diuretics; glucagon; isoniazid; oestrogens and progestogens (e.g. in oral contraceptives); protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine); phenothiazine derivatives; somatropin; sympathomimetic agents (e.g. epinephrine {adrenaline}, salbutamol, terbutaline) and thyroid hormones.

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of OPTISULIN.

Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

PREGNANCY AND LACTATION

OPTISULIN should not be used in pregnancy and mothers on OPTISULIN should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE

General:

OPTISULIN is given subcutaneously once daily. It may be administered at any time during the day, however, at the same time every day.

The desired blood glucose levels as well as the doses and the timing of any antidiabetic medication, including OPTISULIN, must be determined and adjusted individually.

Dose adjustment may also be required, for example, if the patient's weight or lifestyle changes, change in timing of the OPTISULIN dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (refer to “WARNINGS AND SPECIAL PRECAUTIONS”).

Any change to the OPTISULIN dose should be made cautiously and only under medical supervision.

Administration:

OPTISULIN is administered by subcutaneous injection.

OPTISULIN is not intended for intravenous administration.

The prolonged duration of action of OPTISULIN is dependent on its injection into subcutaneous tissue.

Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

Injection sites must be rotated within a given injection area from one injection to the next.

OPTISULIN must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation. Since OPTISULIN is a solution, it does not require resuspension before use. Inspect the vial or cartridge before use. It must only be used if the solution is clear, colourless with no solid particles visible, and if it is of water-like consistency.

Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection. The instructions for using the disposable pens and reusable pens must be followed carefully. Empty cartridges must not be refilled.

If the reusable pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 units per ml) and injected.

Geriatric use: In elderly patients with diabetes, it is recommended that the initial dosing, dose increments, and maintenance dosage be conservative to avoid hypoglycaemic reactions. Hypoglycaemia may be difficult to recognise in the elderly (refer to either “SIDE EFFECTS” or “WARNINGS AND SPECIAL PRECAUTIONS”).

Changeover to OPTISULIN:

The initial dose of OPTISULIN should be determined individually, depending on the desired blood glucose levels.

When changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with OPTISULIN, a change of the dose of the basal insulin is often required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic agents).

When patients are transferred from twice-daily NPH insulin to OPTISULIN administered once daily, to reduce the risk of hypoglycaemia, the initial dose should usually be reduced by approximately 20 % (daily units of OPTISULIN compared to total daily units of NPH insulin) and then the regimen should be adjusted individually.
A programme of close metabolic monitoring is recommended during changeover and in the initial weeks thereafter. This is particularly true for patients on human insulin receiving high doses due to the production of human insulin antibodies.

With improved metabolic control and resulting increase in insulin sensitivity, a further adjustment in dosage regimen may become necessary. Dose adjustment may also be required, for example, if the patient's weight or life-style changes or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (refer to "WARNINGS AND SPECIAL PRECAUTIONS").

Incompatibilities:

OPTISULIN must not be mixed with any other product.

It is important to ensure that syringes must not contain any other medicinal product or residue.

SIDE EFFECTS

The following frequency rating has been used:

Very common: (≥ 1/10); Common: (≥ 1/100, < 1/10); Uncommon: (≥ 1/1000, < 1/100); Rare: (≥ 1/10 000, < 1/1000); Very rare: (< 1/10 000), including rare isolated cases.

Immune system disorders

Rare: Systemic allergic reactions

Immediate-type allergic reactions to OPTISULIN are rare. Such reactions to OPTISULIN or the excipients may, for example, be associated with generalised skin reactions, angioedema, bronchospasm, hypotension and shock, and may be life-threatening.

Endocrine disorders:

Very common: Hypoglycaemia

Hypoglycaemia, in general is the most frequent adverse reaction of OPTISULIN therapy and may occur if the OPTISULIN dose is too high in relation to the insulin requirement.

The following side effects have been reported and the frequencies are unknown:

OPTISULIN administration may cause neutralising insulin antibodies to form. The presence of such insulin antibodies may necessitate adjustment of the OPTISULIN dose in order to correct a tendency to hyper- or hypoglycaemia.

General disorders and administration site conditions:

Common: Injection site reactions and local hypersensitivity reactions

In clinical studies, reactions at the injection site were observed in 3 to 4 % of patients. Such reactions include redness, pain, itching, hives, swelling or inflammation. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Skin and subcutaneous tissue disorders:

Common: Lipohypertrophy

Lipohypertrophy was observed in 1 to 2 % of patients.

Uncommon: Lipoatrophy

Lipoatrophy was uncommon.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (lipodystrophy).

Eye disorders:

The following side effects have been reported and the frequencies are unknown.

A marked change in glycaemic control may cause visual impairment, due to temporary alteration in the turgidity and refractive index of the lens. Intensification of OPTISULIN therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Metabolism disorders:

Rare: OPTISULIN may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified OPTISULIN therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms:

OPTISULIN overdose may lead to severe and sometimes prolonged and life-threatening hypoglycaemia.

Management:

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates.

Adjustments in drug dosage, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

IDENTIFICATION

3 ml cartridge: a clear, colourless solution for injection, in a type I colourless glass cartridge.

10 ml vial: a clear, colourless solution for injection, in a type I colourless glass vial, with a tear-off lid.

PRESENTATION

3 ml cartridge:

Packs containing 5 x 3 ml cartridges containing 3 ml of solution, to be used in conjunction with a reusable pen.

Packs containing 5 x disposable pens, each with a 3 ml cartridge containing 3 ml of solution.

10 ml vial:

Packs containing 1 x 10 ml vial containing 10 ml of solution.

STORAGE INSTRUCTIONS

Store between 2 °C and 8 °C, away from direct light. Do not freeze. Ensure that the container is not directly touching the freezer compartment or freezer packs.

Once in use the cartridge, vial or disposable pen may be stored up to 30 °C for 4 weeks. The unused portion must be discarded. The reusable pen containing a cartridge must not be stored in the refrigerator.

Keep vial in original carton. It is recommended that the date of the first withdrawal from the vial be noted on the label.

Keep out of reach of children.

REGISTRATION NUMBER

41/21.1/0363

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