Professional Information for OPTISULIN®

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OPTISULIN®, 100 IU/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE 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.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adults, adolescents and children aged 2 years and older with diabetes mellitus, where treatment with insulin is required.

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4.2 Posology and method of administration

Posology:

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 medicine, including OPTISULIN, must be determined and adjusted individually.

Dose adjustment may also be required, for example, if the patient's weight or lifestyle changes, or change in timing of the OPTISULIN dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (see section 4.4).

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

Special populations:

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 (see section 4.4 and 4.8).

Paediatric population:

The safety and efficacy of OPTISULIN in children under the age of 2 years have not been established. OPTISULIN should not be used in children under 2 years.

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).

To reduce the risk of hypoglycaemia, when patients are transferred from once daily insulin glargine 300 units/mL to once daily OPTISULIN, the recommended initial OPTISULIN dose is 80 % of insulin glargine 300 units/mL dose that is being discontinued.

When patients are transferred from twice-daily neutral protamine hagedorn (NPH) insulin to OPTISULIN administered once daily, to reduce the risk of nocturnal and early morning 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 (see section 4.4).

Method of 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 to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localised cutaneous amyloidosis.

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.

4.3 Contraindications

OPTISULIN must not be used in:

- Patients hypersensitive to insulin glargine or any of the excipients listed in section 6.1.
- Children < 2 years of age, as in this group efficacy and safety have not been demonstrated.

4.4 Special warnings and precautions for use

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

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localised cutaneous amyloidosis (see section 4.8). 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, and dose adjustment of antidiabetic medicines may be considered.

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 medicines (see section 4.5).

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: AllStar. They should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pen.

Medicine errors:

Medicine errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of OPTISULIN. Insulin label must always be checked before each injection to avoid medicine errors between OPTISULIN and other insulins.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicines (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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

For insulin glargine, as in OPTISULIN, no clinical data on exposed pregnancies from controlled

clinical studies are available. A large amount of data on pregnant women (more than 1 000 pregnancy outcomes) indicates no specific adverse effects of insulin glargine on pregnancy and no specific malformities nor feto/neonatal toxicity of insulin glargine, as in OPTISULIN. Animal data do not indicate reproductive toxicity.

OPTISULIN can be used during pregnancy, if clinically needed.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycaemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breastfeeding:

Breastfeeding women may require adjustments in insulin dose and diet.

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 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.

4.8 Undesirable 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.

Frequency 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.

Metabolism and nutrition disorders:

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

Eye disorders:

Frequency unknown: A marked change in glycaemic control may cause temporary 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.

Skin and subcutaneous tissue disorders:

Common: Lipohypertrophy.

Lipohypertrophy was observed in 1 to 2 % of patients.

Uncommon: Lipoatrophy.

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

Frequency unknown: Localised cutaneous amyloidosis at the injection site has occurred. Hyperglycaemia has been reported with repeated insulin injections into areas of cutaneous amyloidosis; hypoglycaemia has been reported with a sudden change to an unaffected injection site.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of OPTISULIN is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the “Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Side effects can be reported directly to Sanofi’s Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

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4.9 Overdose

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 neurological 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.1 Insulin preparations

Pharmacotherapeutic groups: Drugs used in diabetes, insulins and analogues for injection, long-acting

ATC codes: A10AE04

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.

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial (Study 4032) was an international, multicentre, randomised, 2 x 2 factorial design study conducted in 12 537 participants with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or early type 2 diabetes mellitus and evidence of cardiovascular disease.

Participants were randomised to receive insulin glargine (n=6 264), titrated to a fasting plasma glucose (FPG) of 95 mg/dL (5,3 mM) or less, or Standard Care (n=6 273).

At baseline participants had a mean age of 63,5 years, mean duration of diabetes of 5,8 years in those with pre-existing diabetes, and mean HbA1c of 6,4 %.

Median duration of follow-up was approximately 6,2 years.

At the end of the trial 81 % of participants randomised to take insulin glargine were still on treatment.

Median on-treatment HbA1c values ranged from 5,9 to 6,4 % in the insulin glargine group, and 6,2 to 6,6 % in the Standard Care group throughout the duration of follow-up.

Median FPG in the insulin glargine group was at target (≤ 95 mg/dL) following dose titration for the duration of the study.

The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1,05 for insulin glargine and 0,30 for the Standard Care group.

Overall, severe hypoglycaemia was reported for 3,7 % of these participants over the course of this 6-year study (approximately 0,6 % per participant-year).

The median of the change in body weight from baseline to the last on-treatment visit was 2,2 kg greater in the insulin glargine group than in the Standard Care group.

The primary objective of this trial was to examine the effect of insulin glargine on two co-primary composite efficacy outcomes.

The first one was the time to the first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke, and the second one was the time to the first occurrence of any of the first co-primary events, or revascularisation procedure (cardiac, carotid, or peripheral), or hospitalisation for heart failure.

Secondary endpoints were:

- All-cause mortality
- A composite microvascular outcome
- Development of type 2 diabetes, in participants with IGT and/or IFG at baseline

The primary and secondary outcome results, as well as the results for each component of the coprimary outcomes, are displayed in the two tables below (Table 1 for the time-to-event analyses, and Table 2 for the non-time-to-event analysis of development of diabetes).

Table 1: ORIGIN: Time to onset of each primary and secondary endpoint

	OPTISULIN N=6 264	Standard care N=6 273	Hazard ratio (95 % CI)
Primary endpoints			
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke	1041 (16,6)	1013 (16,1)	1,02 (0,94, 1,11)
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, or hospitalisation for heart failure or	1792 (28,6)	1727 (27,5)	1,04 (0,97, 1,11)

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revascularisation procedure			
Secondary endpoints			
All-cause mortality	951 (15,2)	965 (15,4)	0,98 (0,90, 1,08)
Composite microvascular outcome*	1 323 (21,1)	1 363 (21,7)	0,97 (0,90, 1,05)
Components of co-primary endpoint			
CV death	580 (9,3)	576 (9,2)	1,00 (0,89, 1,13)
MI (fatal or nonfatal)	336 (5,4)	326 (5,2)	1,03 (0,88, 1,19)
Stroke (fatal or nonfatal)	331 (5,3)	319 (5,1)	1,03 (0,89, 1,21)
Revascularisations	908 (14,5)	860 (13,7)	1,06 (0,96, 1,16)
Hospitalisation for heart failure	310 (4,9)	343 (5,5)	0,90 (0,77, 1,05)

* With components of: laser photocoagulation or vitrectomy or blindness for diabetic retinopathy; progression in albuminuria; or doubling of serum creatinine or development of the need for renal replacement therapy.

Table 2: Incidence rate of diabetes by end of study oral glucose tolerance test (OGTT*)

Treatment (N)	OPTISULIN (6 264)	Standard care (6 273)
Number of participants**	737	719
# participants who developed diabetes (%)	182 (24,7)	224 (31,2)

Odds ratio (95 % CI)	0,72 (0,58 to 0,91)

* End of study OGTT was performed 3 – 4 weeks after discontinuing insulin glargine.

** Participants with prediabetes (IFG or IGT) at baseline, based on an OGTT performed then.

There were no statistically significant differences between treatment groups in the overall incidence of cancer (all types combined) or death from cancer.
The time to first event of any cancer or new cancer during the study was similar between the two treatment groups with respective hazard ratios of 0,99 (0,88, 1,11) and 0,96 (0,85, 1,09).
Participation in ORIGIN for a median of approximately 6,2 years showed that treatment with insulin glargine did not alter the risk for cardiovascular outcomes, all-cause mortality or cancer, when compared to standard glucose-lowering therapy.
In addition, metabolic control was maintained at a lower level of glycaemia, with a decrease in the percentage of participants developing diabetes, at a cost of a modest increase in hypoglycaemia and weight gain.

5.2 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 microprecipitates 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Hydrochloric acid

Metacresol

Polysorbate 20 (only in the 10 mL vial)

Sodium hydroxide

Water for injection

Zinc chloride.

6.2 Incompatibilities

OPTISULIN must not be mixed with any other product.

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

6.3 Shelf life

Unopened/not in use:

3 mL *cartridge:* 36 months

10 mL *vial:* 36 months

Opened/in use:

4 weeks

6.4 Special precautions for storage

Unopened/not in use:

Store between 2 °C and 8 °C.

Unopened/not in use and opened/in use cartridges and vials:

Store away from direct light.

Do not freeze, discard if frozen.

Ensure that OPTISULIN is not directly touching the freezer compartment or freezer packs.

Opened/in use cartridges, vials and disposable pens:

Once in use the cartridge, vial or disposable pen may be stored at or below 30 °C for 4 weeks.

Opened cartridges and vials, whether or not refrigerated, must be discarded after 4 weeks from the first use.

Unrefrigerated cartridges and vials, whether in use or not, must be discarded after 4 weeks.

The reusable pen containing a cartridge, or the pen in use must not be stored in the refrigerator.

The unused portion of the cartridge or vial must be discarded.

Keep the vial in original carton.

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

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

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.

Insulin label must always be checked before each injection to avoid medicine errors between OPTISULIN and other insulins (see section 4.4).

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

41/21.1/0363

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 June 2009

10. DATE OF REVISION OF THE TEXT

31 March 2025

Signed: EB