AUSTRALIAN PRODUCT INFORMATION – OPTISULIN/OPTISULIN SOLOSTAR (INSULIN GLARGINE)

1 NAME OF THE MEDICINE

Insulin glargine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Optisulin 3mL cartridge contains 3mL of insulin glargine 100 units/mL.

Optisulin pre-filled pen contains 3mL of insulin glargine 100 units /mL.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Optisulin is a clear to colourless, particle free solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Insulin glargine is an insulin analogue indicated for once-daily subcutaneous administration in the treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Optisulin is an insulin analogue, equipotent to human insulin, with a peakless glucose lowering profile and a prolonged duration of action that permits once daily dosing.

Optisulin is for individual patient use only.

Dosage

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

Optisulin is not intended for intravenous administration.

Blood glucose monitoring is recommended for all individuals with diabetes. The desired blood glucose levels as well as the doses and timing of any antidiabetic medication, including Optisulin, must be determined and adjusted individually. In a clinical study in insulin-naïve patients with type 2 diabetes, Optisulin was started at a dose of 10.8 ± 4.9 IU (mean ± SD; median dose 10 IU) Optisulin once daily and subsequently adjusted individually.

Dose adjustment may also be required, for example, if the patient's weight or lifestyle change, change in timing of insulin dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia. Any change of insulin dose should be made cautiously and only under medical supervision.

Dosage in paediatrics

Optisulin can be safely administered to paediatric patients >6 years of age. In a study comparing Optisulin to NPH insulin in children from 2-5 years, non-inferiority was not demonstrated in relation to the primary outcome of hypoglycaemia (see Section 5.1 Pharmacodynamic Properties – clinical trials). Efficacy in terms of HbA1C (a secondary efficacy endpoint) was similar between groups.

Based on the result of a study in paediatric patients, the dose recommendation for changeover to Optisulin is the same as described for adults.

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, the amount and timing of a short-acting insulin or fast-acting insulin analogue or the dose of any oral antidiabetic drug may need to be adjusted.

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 approximately 80% of the insulin glargine 300 units/mL that is being discontinued.

In clinical studies, when adult patients were transferred from once daily NPH human insulin or ultralente human insulin to once daily Optisulin, the initial dose was usually not changed. In studies when patients were transferred from twice-daily NPH human insulin to Optisulin once daily at bedtime, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) within the first week of treatment and then adjusted based on patient response. There was also a slightly higher rate of injection site pain seen with Optisulin, possibly related to the acidic nature of insulin glargine when compared with NPH insulin. The majority of injection site reactions were mild, with only one subject in each of the Optisulin and NPH treatment groups discontinuing study medication due to injection site adverse events.

A programme of close metabolic monitoring under medical supervision is recommended during changeover and in the initial weeks thereafter. As with all insulin analogues, this is particularly true for patients who, due to antibodies to human insulin, need high insulin doses and may experience markedly improved insulin response with insulin glargine.

With improved metabolic control and resultant increase in insulin sensitivity (reduced insulin requirements) further adjustment of the dose of Optisulin and other insulin or oral antidiabetic agents in the regimen may become necessary.

Method of administration

Although absorption of Optisulin does not differ between abdominal, thigh or deltoid subcutaneous injection sites, as with all insulins, injection sites must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy and localised cutaneous amyloidosis. (see Section 4.4 Special warnings and precautions for use and 4.8 Adverse Effects (Undesirable Effects).

Before first use

Before first use, Optisulin must be kept at room temperature for 1 to 2 hours.

Optisulin must only be used if the solution is clear, colourless with no particles visible, and if it is of water-like consistency.

An empty cartridge or pre-filled pen must never be reused and must be properly discarded.

Optisulin must not be mixed with any other insulin nor be diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Cartridges and pre-filled pens

Manufacturer instructions for using Optisulin in reusable or pre-filled disposable injection devices must be followed carefully for loading the cartridge into a reusable pen, and for attaching the needle, performing the safety test and administering the insulin injection. If the injection device is damaged, it should be discarded and a new injection device should be used.

If the reusable injection device malfunctions (see instructions for using the pen), or no pen is available, Optisulin may be withdrawn from the cartridge into a U100 syringe and injected subcutaneously. The syringe must not contain any other medicinal product or residue.

Pens to be used with Optisulin cartridges

Optisulin cartridges should only be used with the following pens:

- AllStar and AllStar Pro which deliver Optisulin in 1 unit dose increments; or
- JuniorSTAR which delivers Optisulin in 0.5 unit dose increments from 1 unit; or
- ClikSTAR which delivers Optisulin in 1 unit dose increments.

Optisulin cartridges should not be used with any other reusable pen as dosing accuracy has only been established with the listed pens.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycaemia and hyperglycaemia management. Patients

must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate food intake or skipped meals.

Accidental mix-ups between insulin glargine and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between insulin glargine and other insulins, patients should be instructed to always check the insulin label before each injection.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycaemia or hyperglycaemia.

4.3 CONTRAINDICATIONS

Optisulin must not be used in patients hypersensitive to insulin glargine or any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Optisulin must not be diluted or mixed with any other insulin or solution.

Optisulin is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous space. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

As with all insulins, the time course of Optisulin action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature and physical activity.

Patients, and if appropriate, their relatives, must also be alert to the possibility of hyper- or hypoglycaemia, and know what actions to take.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's compliance with all prescribed treatment regimens, injection sites and proper injection technique, the handling of the pen and all other relevant factors must be reviewed before dose adjustment is considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localised 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, and dose adjustment of antidiabetic medications may be considered (See Section 4.8 Adverse Effects (Undesirable Effects).

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating becoming pregnant.

Diabetic ketoacidosis

Optisulin is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, intravenous human insulin is recommended in such cases.

Hypoglycaemia

As with all insulins, particular caution (including intensified blood glucose monitoring) should be exercised in patients who are at greater risk of clinically significant sequelae from hypoglycaemic episodes.

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

In clinical studies, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after insulin glargine and human insulin both in healthy volunteers and patients with type I diabetes. However, the warning symptoms of hypoglycaemia may be changed, be less pronounced, or be absent in certain risk groups, as for example, in patients whose glycaemic control is markedly improved; in elderly patients; where an autonomic neuropathy is present; in patients with a long history of diabetes; in patients receiving concurrent treatment with certain other drugs.

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

Hypoglycaemia is the most common adverse effect of insulins. The incidence of nocturnal hypoglycaemia in regimens that include insulin glargine is significantly reduced in patients with type 2 diabetes compared with regimens containing NPH human insulin. The time of occurrence of hypoglycaemia depends on the action profile of the insulins and may, therefore, change when the treatment regimen is changed.

Use in hepatic impairment

Although no studies have been performed in patients with diabetes and hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Use in renal impairment

Although no studies were performed in patients with renal impairment, insulin requirements may be diminished because of reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Use in the elderly

Progressive deterioration of renal function may lead to a steady decrease in insulin requirements. Furthermore, the warning signs of hypoglycaemia may be changed, diminished or absent in elderly patients. See Section 4.4 Special warnings and precautions for use, Hypoglycaemia, and Section 5.2 Pharmacokinetic properties, Special populations.

Use with intercurrent conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances or stress.

Age and gender

There were no phase 1 studies to evaluate the effects of age and race. In clinical trials, subgroup analysis based on age and gender did not indicate any difference in safety and efficacy in insulin glargine treated patients compared to the total study population.

Obesity

In clinical trials, subgroup analysis based on BMI showed no differences in safety and efficacy in insulin glargine treated patients compared to the total study population. The same was true for NPH insulin.

Paediatric use

In general, the safety profile for patients ≤18 years of age is similar to the safety profile for patients >18 years. The adverse events reports received from Post Marketing Surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in patients ≤18 years of age than in patients >18 years.

Data from pooled clinical trials in adults and children aged 6 to 18 years did not show a greater incidence of either injection site reaction or skin reactions in the paediatric population compared to adults.

Pharmacokinetics in children aged 2 to less than 6 years of age with type 1 diabetes mellitus was assessed in one clinical study. Plasma “trough” levels of insulin glargine and its main metabolites M1 and M2 were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Substances that may enhance the blood glucose lowering effect and susceptibility to hypoglycaemia

Oral antidiabetic agents, ACE inhibitors, pentoxifylline, perhexiline, disopyramide, fibrates, fluoxetine, MAO inhibitors, dextropropoxyphene, salicylates, sulfonamide antibiotics.

Substances that may reduce the blood glucose lowering effect

Corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, estrogens, progestogens, oral contraceptives, phenothiazine derivatives, somatotrophin, sympathomimetic agents (eg adrenaline (epinephrine), salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (eg olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may be sometimes followed by hyperglycaemia.

Others

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a combined fertility, prenatal and postnatal study in male and female rats at subcutaneous doses up to 10 IU/kg/day (approximately 5 times anticipated clinical exposure based on BSA), insulin glargine was maternotoxic due to dose-dependent hypoglycaemia leading to death at the highest dose. There were no effects of treatment on fertility. Similar effects were seen with NPH insulin.

Use in pregnancy

Category B3.

There are no randomised controlled clinical studies of the use of insulin glargine in pregnant women.

A large number (more than 1000 retrospective and prospective pregnancy outcomes with Optisulin) of exposed pregnancies from Post Marketing Surveillance indicate no specific adverse effects on pregnancy or on the health of the foetus and newborn child.

Furthermore a meta-analysis of eight observational clinical studies including 331 women using Optisulin and 371 women using insulin NPH was performed to assess the safety of insulin glargine and insulin NPH in gestational or pregestational diabetes. No significant differences in safety-related maternal or neonatal outcomes were seen between insulin glargine and insulin NPH during pregnancy.

It is essential to maintain good control of the insulin-treated patient (insulin-dependent or gestational diabetes) throughout pregnancy to prevent adverse outcomes associated with hyperglycaemia. Insulin requirements usually fall during the first trimester, increase during

the second and third trimesters and rapidly decline after delivery. Careful monitoring of glucose control is essential.

Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy and insulin glargine should be used during pregnancy only if the potential benefits outweigh potential risk.

Embryofetal development studies in rats and rabbits have been performed at subcutaneous doses up to 20 IU/kg/day and 2 IU/kg/day, respectively (approximately 10 times and twice anticipated clinical exposure, respectively, based on BSA). The effects of insulin glargine generally did not differ from those observed with NPH insulin in rats or rabbits. However, in rabbits dosed with 2 IU/kg/day there was an increased incidence of dilatation of the cerebral ventricles.

Use in lactation

It is not known whether insulin glargine is excreted in significant amounts in human milk or animal milk. Many drugs, including insulin, are excreted in human milk. For this reason, caution should be exercised when insulin glargine is administered to a nursing mother. Lactating women may require adjustments in insulin dose and diet.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Table 1 - Adverse Events in Phase 2/3 Trials (> 2%) Adults

	NPH (n= 1784)	Optisulin (n= 2106)
Upper respiratory infection	330 (18.5%)	367 (17.4%)
Infection	178 (10.0%)	182 (8.6%)
Accidental injury	97 (5.4%)	101 (4.8%)
Headache	74 (4.1%)	103 (4.9%)
Injection site haemorrhage	81 (4.5%)	89 (4.2%)
Retinal vascular disorder	81 (4.5%)	82 (3.9%)
Gastroenteritis	64 (3.6%)	68 (3.2%)
Sinusitis	62 (3.5%)	68 (3.2%)
Rhinitis	63 (3.5%)	61 (2.9%)
Back pain	48 (2.7%)	57 (2.7%)
Injection site pain	13 (0.7%)	55 (2.6%)
Hypoglycaemic reaction	61 (3.4%)	54 (2.6%)
Neuropathy	45 (2.5%)	53 (2.5%)

	NPH (n= 1784)	Optisulin (n= 2106)
Peripheral oedema	32 (1.8%)	42 (2.0%)
Urinary tract infection	35 (2.0%)	41 (1.9%)

Table 2 - Summary of symptomatic hypoglycaemic results in Phase 3 study in patients aged 2-6 years

Event rate (Per patient year)	Optisulin	NPH	Event ratio (95% CI)
Symptomatic hypoglycaemia	25.54	33.02	0.76 (0.46 to 1.25).

Table 3 - Cardiovascular and Cancer Events in ORIGIN

	Optisulin N=6264	Standard Care N=6273	Optisulin vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Cardiovascular			
Co-primary endpoints			
CV death, non-fatal myocardial infarction, or nonfatal stroke	1041 (2.9)	1013 (2.9)	1.02 (0.94, 1.11)
CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure or revascularisation procedure	1792 (5.5)	1727 (5.3)	1.04 (0.97, 1.11)
Components of co-primary endpoints			
CV death	580	576	1.00 (0.89, 1.13)
Myocardial Infarction (fatal or non-fatal)	336	326	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331	319	1.03 (0.89, 1.21)
Revascularisations	908	860	1.06 (0.96, 1.16)
Hospitalisation for heart failure	310	343	0.90 (0.77, 1.05)
Cancer			
Cancer endpoints			
Any cancer event (new or recurrent)	559 (1.56)	561 (1.56)	0.99 (0.88, 1.11)
New cancer events	524 (1.46)	535 (1.49)	0.96 (0.85, 1.09)

	Optisulin N=6264	Standard Care N=6273	Optisulin vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Death due to Cancer	189 (0.51)	201 (0.54)	0.94 (0.77, 1.15)

Over the course of this 6 year study severe hypoglycaemia was reported in 5.7% of the Optisulin group compared to 1.9% of the Standard Care group. The rates (per 100 Patient-Years) of confirmed all hypoglycaemia events, severe hypoglycaemia events and non-severe symptomatic hypoglycaemia are shown in Table 4 below.

Over the course of this 6-year study, 42% of the Optisulin group and 74% of the Standard Care group did not experience any hypoglycaemia.

Table 4 - Severe, Non-severe and All symptomatic Hypoglycaemia in the ORIGIN Trial

	Optisulin		Standard Care	
	Number (%) of affected patients	Number per 100 pt-yr	Number (%) of affected patients	Number per 100 pt-yr
Severe hypoglycaemia	352 (5.7%)	1.05	113 (1.9%)	0.30
Non-severe hypoglycaemia	3533 (57%)	10.6	1582 (25%)	4.3
All	3597 (58%)	10.7	1624 (26%)	4.4

The median of the change in body weight from baseline to the last on-treatment visit was 2.2kg greater in the Optisulin group than in the Standard Care group i.e. weight gain of 1.4kg in Optisulin group compared to weight loss of 0.8kg in standard care group.

Hypoglycaemia

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

As with all insulins, severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopaenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Eyes

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

As with all insulin regimens, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary visual impairment or worsening of diabetic retinopathy. However, long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient partial or complete blindness.

Retinopathy was evaluated in clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for Optisulin and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In a 5-year NPH-controlled study, the primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. The results of this analysis are shown in Table 5 for both the per-protocol (primary) and Intent-to-Treat (ITT) populations, and indicate non-inferiority of Optisulin to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 5 - Number (%) of Patients with 3 or More Step Progression on ETDRS Scale at Endpoint

	Optisulin (%)	NPH (%)	Difference a,b (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-1.98% (2.57%)	-7.02% to 3.06%
Intent-to Treat	63/502 (12.5%)	71/487 (14.6%)	-2.10% (2.14%)	-6.29% to 2.09%

a Difference = Optisulin - NPH

b Using a generalised linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function

Skin and subcutaneous tissue disorders

As with any insulin therapy, lipodystrophy may occur at the injection site and delay local insulin absorption. In clinical studies, in regimens, which included insulin glargine, lipohypertrophy was observed in 1 to 2 % of patients, whereas lipoatrophy was uncommon.

Localised cutaneous amyloidosis at the injection site has occurred with insulins. 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.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. (see section 4.4 Special warnings and precautions for use).

Injection site and allergic reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling and inflammation. Most minor reactions to insulins usually resolve in a few days to a few weeks.

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

Animal studies with insulin glargine have identified significant local tolerance toxicity at the injection site following repeat subcutaneous administration. Care should be taken to rotate the site of injection.

Antibody production

Insulin administration may cause the formation of antibodies to insulin. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both NPH human insulin and insulin glargine treatment groups with similar incidences. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

Other reactions

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Medication errors have been reported in which other insulins have been accidentally administered instead of insulin glargine.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

An excess of insulin relative to food intake, energy expenditure or both 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 exercise may be needed.

More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycaemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycaemia.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, Insulins and analogue for injection, long-acting, ATC code: A10AE04.

Mechanism of action

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Pharmacodynamics

Insulin glargine is a human insulin analogue that has been designed to have low solubility at neutral pH. At pH 4, the pH of the Optisulin injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralised, leading to formation of microprecipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable time/concentration profile and a prolonged duration of action. This allows once daily dosing to meet a patient's basal insulin needs.

Insulin glargine is metabolised into 2 active metabolites M1 and M2.

Insulin receptor binding:
In vitro studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

IGF-1 receptor binding:
The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin.

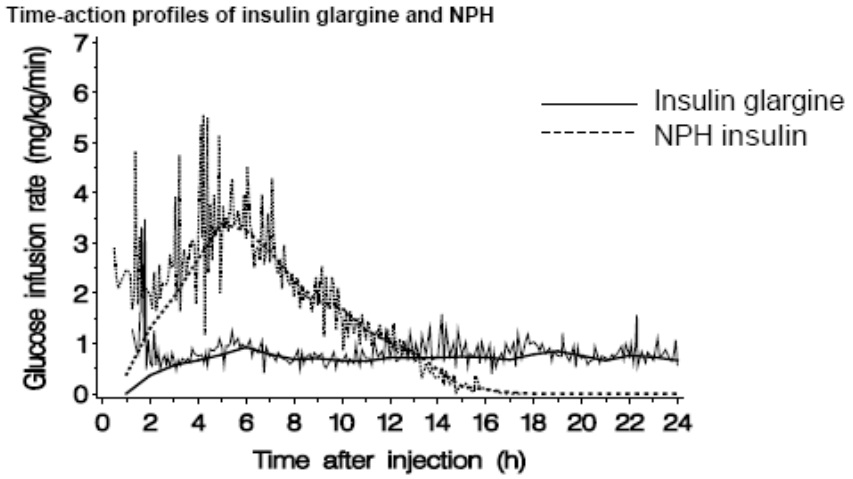
The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in Optisulin therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

In clinical studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses.

In euglycaemic clamp studies in healthy subjects or in patients with type I diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH (Neutral Protamine Hagedorn) human insulin. The effect profile of insulin glargine was smooth and peakless, and the duration of its effect was prolonged compared to NPH human insulin. Figure 1 shows results from a study in patients with type I diabetes. The median time between injection and

the end of pharmacological effect was 14.5 hours for NPH human insulin, and 24 hours (the end of the observation period) for insulin glargine.

Figure 1



Mean GIR in subjects with type 1 diabetes mellitus after a single sc injection of 0.3 IU/kg insulin glargine or NPH (hourly mean data [n = 20] derived from, and superimposed on, smoothed original clamp data [where n ≥ 5] obtained at intervals of about five to ten minutes)

The longer duration of Optisulin is directly related to its slower rate of absorption and supports once daily subcutaneous administration. The time course of action of insulin and insulin analogues such as Optisulin may vary considerably in different individuals or within the same individual but is, due to the lack of a peak, less variable with insulin glargine than with NPH insulin.

Clinical trials

Efficacy studies

The overall efficacy of once-daily Optisulin on metabolic control was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomised, active-control, parallel studies of 2327 adult patients and 349 paediatric patients with type 1 diabetes mellitus and 1563 patients with type 2 diabetes mellitus.

Type 1 diabetes in adults (see Table 9)

In Phase 3 studies, patients with type 1 diabetes (Studies 3001 and 3004, n=1119) were randomised to basal-bolus treatment with Optisulin once daily or to NPH human insulin once or twice daily and treated for 28 weeks. Regular human insulin was administered before each meal. Optisulin was administered at bedtime. NPH human insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily. Optisulin had a larger effect in reducing fasting glucose than NPH human insulin administered twice daily, but was comparable with NPH human insulin twice daily in its effect on glycohaemoglobin (GHb) and incidence of nocturnal and severe hypoglycaemia. Compared to once daily NPH human insulin, Optisulin had a similar effect on fasting glucose and GHb. Hypoglycaemia was reported with similar frequency during the first month of the studies (during initial titration period) after starting treatment with Optisulin compared to NPH human insulin.

In another Phase 3 study, patients with type 1 diabetes (Study 3005, n=619) were treated for 16 weeks with a basal-bolus insulin regimen where insulin lispro was used before each meal. Optisulin was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Optisulin and NPH human insulin had a similar effect on GHb, with similar numbers of patients reporting a hypoglycaemic episode.

Type 1 diabetes in children (see Table 10)

In a randomised, controlled clinical study, paediatric patients (ranging in age from 6 to 15 years) with type 1 diabetes (Study 3003, n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Optisulin was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on GHb and the incidence of hypoglycaemia were observed in both treatment groups.

Type 1 paediatric diabetes (2 to 6 years)

A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 1 to 6 years (61 children from 2 to 5 in the insulin glargine group and 64 children from 1 to 6 in the NPH insulin group), comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin. Both groups received bolus insulin before meals.

Comparison of the two treatment regimens in terms of hypoglycaemia was the primary objective of the study. The composite primary outcome consisted of: continuous glucose monitoring excursions below 3.9mmol/L, confirmed by fingerstick blood glucose (FSBG) measurements; other FSBG measurements < 3.9mmol/L; and episodes of symptomatic hypoglycaemia.

Overall, the event rate ratio of this composite outcome for once daily Optisulin compared to NPH (given twice daily in most patients) was 1.18 (95% CI: 0.97-1.44), therefore, not meeting the non-inferiority margin of 1.15.

The rate of symptomatic hypoglycaemia events is the most commonly used and clinically relevant component of the composite outcome. Rates of symptomatic hypoglycaemia events were numerically lower in the insulin glargine group, both overall (25.5 episodes per patient-year, vs 33.0 for NPH) and overnight (2.38 episodes per patient-year, vs 3.65 for NPH).

Glycohaemoglobin and glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this trial.

Table 6 summarises the primary outcome results between Optisulin and NPH insulin.

Table 6 - Summary of the primary outcome results between Optisulin and NPH insulin

Event rate	Optisulin (N=61)	NPH (N=64)
All hypoglycaemia events	192.75	168.91
All symptomatic hypoglycaemia events	25.54	33.02
All low CGM confirmed by a low FSBG	74.61	71.60

Event rate	Optisulin (N=61)	NPH (N=64)
All low CGM	270.31	262.51
All low FSBG	192.69	168.24

Note: On-treatment period for hypoglycaemia is from the first dose of IP up to 24 hours after the last dose of IP

Optisulin has not been studied in children below 2 years.

*Type 2 diabetes in adults (see Table 7***)**

In one Phase 3 study (Study 3002, n=570), Optisulin was evaluated for 52 weeks as part of a regimen of combination therapy with insulin and oral antidiabetic agents (a sulfonylurea, metformin, acarbose, or combinations of these drugs). Optisulin administered once daily at bedtime was as effective as NPH human insulin administered once daily at bedtime in reducing GHb and fasting glucose. However, fewer patients treated with Optisulin reported a nocturnal hypoglycaemic episode after initial titration, from study month 2 to end of study (Table 7).

Table 7- Study report 3002: Patients with nocturnal hypoglycaemia

	Optisulin	NPH	p
Month 2 – Week 20	10.1%	16.9%	0.0195
Week 20 – end of study	5.7%	11.4%	0.0150
Entire treatment	12.1%	24.2%	0.0002

In another Phase 3 study in patients with type 2 diabetes not using oral antidiabetic agents (Study 3006, n=518), a basal-bolus regimen of Optisulin once daily at bedtime or NPH human insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals as needed. Optisulin had similar effectiveness as either once- or twice-daily NPH human insulin in reducing GHb and fasting glucose. Fewer patients treated with Optisulin reported nocturnal hypoglycaemia from study month 2 to end of study (Table 8).

Table 8 - Study report 3006: Patients with nocturnal hypoglycaemia

	Optisulin	NPH	p
Month 2 – end of study	26.5%	35.5%	0.0136
Entire treatment	31.3%	40.2%	0.0160

Type 1 and type 2 adult diabetes

Table 9 compares regimens of Optisulin once daily to NPH human insulin either once or twice daily in subgroups of patients from Phase 3 studies based upon prior basal insulin regimens.

Table 9 - Summary of main therapeutic outcomes of the clinical studies in adults

Type 1 Diabetes Mellitus

Diabetes population	Treatment	Endstudy mean (mean change from baseline)			
		n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L)[a]
Previous use of once-daily basal injection regimen					
with regular human insulin	Optisulin	222	7.98 (0.01)	222	8.4 (-0.9)
	NPH human insulin (once daily)	218	7.95 (-0.05)	218	8.2 (-1.2)
with insulin lispro	Optisulin	73	7.11 (-0.25)	73	8.0 (-1.4)
	NPH human insulin (once daily)	69	7.46 (-0.23)	69	8.7 (-0.9)
Previous use of more than once-daily basal injection regimen					
with regular human insulin	Optisulin	334	7.77 (0.06)	334	7.9 (1.3)[b]
	NPH human insulin (twice daily)	345	7.69 (-0.05)	345	8.7 (-0.7)
with insulin lispro	Optisulin	237	7.66 (-0.03)	237	8.0 (-1.7)[b]
	NPH human insulin (twice daily)	240	7.64 (-0.05)	240	9.1 (-0.6)

Type 2 Diabetes Mellitus

Diabetes population	Treatment	Endstudy mean (mean change from baseline)			
		n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L)a
Insulin in combination with oral antidiabetic agents					
No previous insulin use	Optisulin	216	8.45 (-0.65)	214	7.1 (-3.3)
	NPH human insulin (once daily)	195	8.27 (-0.63)	195	7.4 (-3.1)
Previous insulin use	Optisulin	64	9.12 (0.31)	66	7.2 (-1.1)
	NPH human insulin (once daily)	71	9.15 (0.42)	73	7.4 (-1.1)
Insulin without oral antidiabetic agents					
Previous use of once-daily basal insulin	Optisulin	52	8.07 (-0.34)	52	8.5 (-0.8)
	NPH human insulin (once daily)	48	7.92 (-0.45)	48	7.9 (-1.2)
Previous use of more than once daily basal insulin	Optisulin	207	8.15 (-0.44)	207	7.7 (-1.4)
	NPH human insulin (twice daily)	211	7.96 (-0.61)	211	8.1 (-1.1)

[a] Fasting blood glucose conversion, mg/dL/18=mmol/L

[b] p<0.05; Optisulin compared with NPH human insulin

Type 1 diabetes in children

Table 10 compares regimens of Optisulin once daily to NPH human insulin either once or twice daily in subgroups of patients from Phase 3 studies based upon prior basal insulin regimens.

Table 10 - Summary of Main Therapeutic Outcomes of the Clinical Studies in Children

Type 1 Diabetes Mellitus in Children				
Treatment	**Endstudy mean (mean change from baseline)**			
	n	**Glycated haemoglobin (%)**	**n**	**Fasting blood glucose (mmol/L)**
Previous use of once-daily basal injection regimen				
Optisulin	92	9.15 (0.55)	105	9.99 (-1.34)
NPH human insulin (once daily)	80	9.26 (0.36)	93	10.51 (-0.74)
Previous use of more than once-daily basal injection regimen				
Optisulin	63	8.55 (0.12)	68	8.87 (-1.21)
NPH human insulin (twice daily)	54	8.86 (0.01)	57	9.50 (-0.40)

ORIGIN trial (study HOE901/4032)

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) trial was an international, multicenter, randomised, open-label, 2x2 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 CV disease. Participants were randomised to receive Optisulin (n=6264) (participants with IFG and/or IGT = 11.7%, early type 2 diabetes mellitus = 88.3%), titrated to a FPG of 5.3mmol/L or less, or Standard Care (n=6273) (participants with IFG and/or IGT = 11.4%, early type 2 diabetes mellitus = 88.6%). 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 median 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 Optisulin were still on treatment.

The primary objective of the trial was to demonstrate that Optisulin use could significantly lower the risk of major cardiovascular endpoints compared to standard care. There were two co-primary composite efficacy outcomes. The first one was the time to the first occurrence of CV 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 revascularization 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

After a median treatment duration of 6.2 years, Optisulin did not alter the relative risk for CV disease and CV mortality when compared with standard care. There were no significant differences between Optisulin and standard care for the two co-primary outcomes, for any individual components of the co-primary outcomes, for all-cause mortality or for the composite microvascular outcomes. The results are displayed in the table below.

Table 11 - ORIGIN: Primary and Secondary Outcomes

	Optisulin N=6264	Standard Care N=6273	Optisulin vs Standard Care
	Participants with Events N (%)	Participants with Events N (%)	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 revascularization procedure	1792 (28.6)	1727 (27.5)	1.04 (0.97, 1.11)
Secondary endpoints			
All-cause mortality	951 (15.2)	965 (15.4)	0.98 (0.90, 1.08)
Composite microvascular outcome*	1323 (21.1)	1363 (21.7)	0.97 (0.90, 1.05)
Components of coprimary endpoint			
CV death	580 (9.3)	576 (9.2)	1.00 (0.89, 1.13)
MI (fatal or non-fatal)	336 (5.4)	326 (5.2)	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331 (5.3)	319 (5.1)	1.03 (0.89, 1.21)
Revascularizations	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.

Median on-treatment HbA1c values ranged from 5.9 to 6.4 % in the Optisulin group, and 6.2% to 6.6% in the Standard Care group throughout the duration of follow-up. Median FPG at the end of study in the Optisulin group was 5.4mmol/L, and for the Standard Care group was 6.8mmol/L.

Over the course of this 6 year study severe hypoglycaemia was reported in 5.7% of the Optisulin group compared to 1.9% of the Standard Care group. The rates (per 100 Patient-Years) of confirmed all hypoglycaemia events, severe hypoglycaemia events and non-severe symptomatic hypoglycaemia are shown in Table 12 below:

Over the course of this 6-year study, 42% of the Optisulin group and 74% of the Standard Care group did not experience any hypoglycaemia.

Table 12 - Severe, Non-severe and All symptomatic Hypoglycaemia in the ORIGIN Trial

	Optisulin		Standard Care	
	Number (%) of affected patients	Number per 100 pt-yr	Number (%) of affected patients	Number per 100 pt-yr
Severe hypoglycaemia	352 (5.7%)	1.05	113 (1.9%)	0.30
Non-severe hypoglycaemia	3533 (57%)	10.6	1582 (25%)	4.3
All hypoglycaemia	3597 (58%)	10.7	1624 (26%)	4.4

The median of the change in body weight from baseline to the last on-treatment visit was 2.2kg greater in the Optisulin group than in the Standard Care group i.e. weight gain of 1.4kg in Optisulin group compared to weight loss of 0.8kg in standard care group.

Cancer

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancers was similar between the treatment groups as shown in Table 13 below:

Table 13- Cancer Outcomes in ORIGIN – Time to First event Analyses

	Optisulin N=6264	Standard Care N=6273	Optisulin vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Cancer endpoints			
Any cancer event (new or recurrent)	559 (1.56)	561 (1.56)	0.99 (0.88, 1.11)
New cancer events	524 (1.46)	535 (1.49)	0.96 (0.85, 1.09)
Death due to Cancer	189 (0.51)	201 (0.54)	0.94 (0.77, 1.15)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After subcutaneous injection of insulin glargine in healthy subjects and patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a lack of a peak in comparison to NPH human insulin. However, the assay was unable to differentiate between the two forms of insulin (native human insulin and insulin glargine).

Concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type I diabetes, a flat concentration-time profile has been demonstrated; this is also reflected in the wide range of Tmax values (0 to 22.5 h) compared to 0.3 IU/kg NPH human insulin (2.5 to 10.5 h).

There were no relevant differences in serum insulin glargine levels and the duration of action after abdominal, deltoid or thigh subcutaneous administration.

In a randomised, controlled, double-blind, four-way crossover trial in healthy male volunteers, Optisulin with polysorbate 20 was found to be bioequivalent to Optisulin.

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 (21AGly-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.

Special populations

Age and Gender

There were no phase 1 studies to evaluate the effects of age and race. In clinical trials, subgroup analysis based on age and gender did not indicate any difference in safety and efficacy in insulin glargine treated patients compared to the total study population.

Obesity

In clinical trials, subgroup analysis based on BMI showed no differences in safety and efficacy in insulin glargine treated patients compared to the total study population. The same was true for NPH insulin.

Renal and Hepatic Impairment

No studies were performed in patients with renal or hepatic impairment. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including insulin glargine may be necessary.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Insulin glargine was negative in tests for mutagenicity in bacterial and mammalian cells and for clastogenicity (in vitro in V79 cells and in vivo in Chinese hamsters).

Carcinogenicity

Two year carcinogenicity studies were performed in mice and rats at subcutaneous doses up to 12.5 IU/kg/day (approximately 3 and 7 times anticipated clinical exposure based on BSA). Malignant fibrous histiocytomas were found at insulin glargine injection sites in male rats and mice. The incidence of these tumours was not dose-dependent and tumours were also present at acid vehicle control injection sites but not at saline control injection sites or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Other insulin preparations are known to cause an increase in mammary tumours in female rats. No such increase in tumours was seen with insulin glargine probably because of the lower doses of insulin glargine used in the mouse and rat carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients contained in Optisulin solution are glycerol, hydrochloric acid, metacresol sodium hydroxide for adjustment to pH 4, zinc chloride and water for injection.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See Section 4.5 – interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

See Section 6.4 Special precautions for storage, for shelf life after first use and open (in use) or unrefrigerated cartridges and pre-filled pens.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2 to 8 degrees Celsius. Do not freeze.

Unopened cartridges and pre-filled pens

Unopened cartridges and pre-filled pens (Optisulin SoloStar) should be stored in a refrigerator where the temperature is between +2°C and +8°C. Do not freeze. Discard if frozen. Keep in the outer carton in order to protect from light. Do not store next to the freezer compartment or freezer packs.

Open (in use) or unrefrigerated cartridges and pre-filled pens

Optisulin cartridges or pre-filled pens, whether or not refrigerated, must be discarded after 28 days from first use. Do not freeze. Discard if frozen.

Unrefrigerated cartridges or pre-filled pens, whether or not in use, must be discarded after 28 days. This applies irrespective of whether the cartridge or pre-filled pen is used immediately or is first carried as a spare for a while.

Cartridges and pre-filled pens

Once in use, pre-filled pens (such as Optisulin SoloStar) or a reusable injection pen containing a cartridge of Optisulin must not be stored in the refrigerator. Optisulin that is in use in injection pens may be kept unrefrigerated for up to 28 days, as long as the temperature is not greater than 30˚C and it is kept away from direct heat and light. It must be used within a 28 day period or must be discarded 28 days after commencement of use.

6.5 NATURE AND CONTENTS OF CONTAINER

Optisulin 100 units per mL (U 100) is available as:

- 3mL cartridges
    - 5 pack
- Solostar prefilled disposable devices
    - 5 pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Optisulin is a sterile clear to colourless solution of insulin glargine in cartridges for use as an injection. The 3mL cartridges contain 100 IU/mL (3.6378 mg/mL) insulin glargine.

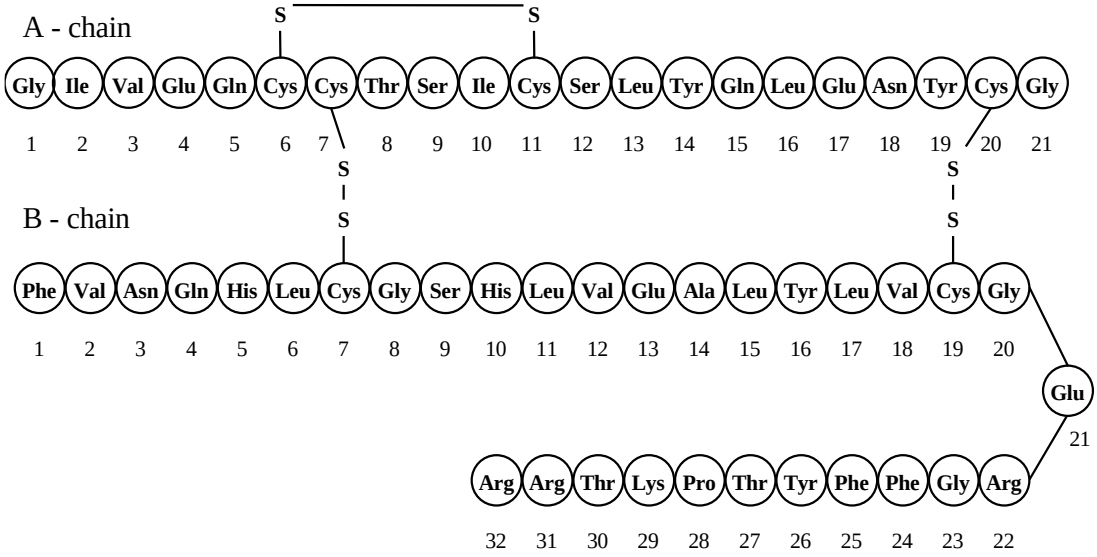
Optisulin [insulin glargine injection {rDNA origin}] is a recombinant human insulin analogue produced by DNA technology. Insulin glargine differs from human insulin in that

the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. The structural formula is shown below:

Molecular Formula: $C_{267}H_{404}N_{72}O_{78}S_6$

Molecular Weight: 6063

Chemical Name: 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin



CAS number

The CAS number is 160337-95-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

Optisulin 3mL cartridge	28 February 2001
Optisulin SoloStar 3mL pre-filled pen	22 June 2006

10 DATE OF REVISION

03 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5	Updating pentoxifylline (oxpentifylline) to pentoxifylline
6.5	Removal of non-marketed pack size
8	Editorial changes to the sponsor details