For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Semglee™
insulin glargine injection
100 units/mL (U-100)

Solution for Subcutaneous Injection

1 prefilled pen with 3 mL cartridge

COMPOSITION

Each mL of prefilled pen contains: Insulin glargine (r-DNA origin) 100 U, m-cresol 2.7 mg/mL (as preservative), Excipients q.s.

Each 3 mL cartridge in a prefilled pen contains insulin glargine* solution for injection, equivalent to 300 units.

*Insulin glargine is produced by recombinant DNA technology in Pichia pastoris.

For the full list of excipients, see "List of Excipients" section.

PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting. ATC Code: A10AE04.

Semglee™ is a biosimilar medicinal product.

Mechanism of action

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 Semglee™ 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 continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section "Pharmacokinetic properties").

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 halfmaximal 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 insulin Glargine therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

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.

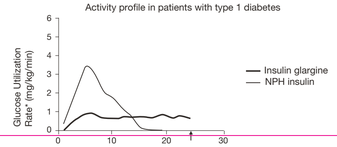
In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables.

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, its effect profile was smooth and peakless, and the duration of its effect was prolonged.

The following graph shows the results from a study in patients: The longer duration of action of subcutaneous 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.

In a clinical study, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after

Activity profile in patients with type 1 diabetes



*determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values)

intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes.

In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed with the same frequency in both NPH-insulin and insulin glargine treatment groups.

Effects of insulin glargine (once daily) on diabetic retinopathy were evaluated in an open-label 5-year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when insulin glargine was compared to NPH insulin.

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomised, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12% of participants) or type 2 diabetes mellitus treated with ≤1 antidiabetic oral agent (88% of participants). Participants were randomised (1:1) to receive insulin glargine (n=6264), titrated to reach FPG ≤95 mg/dl (5.3 mM), or standard care (n=6273).

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

Secondary endpoints included all-cause mortality and a composite microvascular outcome.

Insulin glargine did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co-primary outcomes; for any component endpoint comprising these outcomes; for all-cause mortality; or for the composite microvascular outcome.

Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and 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.

The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6-year study, 42% of the insulin glargine group did not experience any hypoglycaemia.

At the last on-treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.

Paediatric population

In a randomised, controlled clinical study, paediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohemoglobin and the incidence of symptomatic hypoglycemia were observed in both treatment groups, however fasting plasma glucose decreased more from baseline in the insulin glargine group than in the NPH group.

There was less severe hypoglycaemia in the insulin glargine group as well. One hundred forty three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension study with mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.

A crossover study comparing insulin glargine plus lispro insulin to NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed. As in the paediatric study described above, fasting plasma glucose reduction from baseline was greater in the insulin glargine group than in the NPH group.

HbA1c changes from baseline were similar between treatment groups; however blood glucose values recorded overnight were significantly higher in the insulin glargine/ lispro group than the NPH/regular group, with a mean nadir of 5.4 mM versus 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycaemia were 32% in the insulin glargine / lispro group versus 52% in the NPH / regular group.

A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 2 to 6 years, 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.

The primary aim of demonstrating non-inferiority of insulin glargine to NPH in all hypoglycaemia was not met and there was a trend to an increase of hypoglycemic events with insulin glargine [insulin glargine: NPH rate ratio (95% CI) = 1.18 (0.97-1.44)].

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

Pharmacokinetics properties

In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin. Concentrations were thus consistent with the timeprofile of the pharmacodynamic activity of insulin glargine. The graph above shows the activity profiles over time of insulin glargine and NPH insulin.

Insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose.

When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.

After subcutaneous injection of insulin glargine in diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30Bi-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of insulin Glargine.

The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine 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 insulin glargine.

In clinical studies, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy in insulin glargine-treated patients compared to the entire study population.

Paediatric population

Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study (see section "pharmacodynamic properties"). Plasma "trough" levels of insulin glargine and its main M1 and M2 metabolites 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.

Preclinical safety data

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

Comparability of Semglee with Lantus

Semglee insulin glargine, is a biosimilar medicinal product to Lantus insulin glargine. The comparability of Semglee to Lantus has been demonstrated with regard to physiochemical characteristics, efficacy and safety outcomes.

Summary of Clinical Studies

Study ID	Number of Patients	Diagnosis Inclusion Criteria	Primary Endpoints
Study 1	517	Established Type 1 diabetes mellitus18-65 yrs, HbA1c ≤9.5%	Non-inferiority based on change in HbA1c at Week 24
Study 2	490	Established Type 2 diabetes mellitus 18-65 yrs, HbA1c of <10.5% (or >7.5 to ≤10.5% for insulin-naïve patients)	Non-inferiority based on change in HbA1c at Week 24
Study 3	118	Established T1DM patients, who completed 52 wks on Lantus in Study MYL GAI 3001	Equivalence for change in HbA1c at Week 36
Study 4	112	T1DM	To compare the test/reference ratios of the primary PK endpoints: AUCins. 0-30h; Cins.max. primary PD endpoints: AUCGIR0-30h; GIRmax.

Pharmacokinetic (PK) and Pharmacodynamic (PD) Results

Parametric Analysis of Primary and Secondary PK Parameters (PK Analysis Set)

Parameter	Products	Nª	Geometric mean ratio (T/R)	90% CI
Primary PK parameters				
$AUC_{0hj-0-30h}$ [pmol*h/L]	Lantus-EU vs. Lantus-US	51	1.01	0.95 - 1.07
	Semglee vs. Lantus-EU	48	1.02	0.96 - 1.08
	Semglee vs. Lantus-US	44	1.02	0.96 - 1.09
$C_{ins.max}$ [pmol/L]	Lantus-EU vs. Lantus-US	83	1.01	0.95 - 1.08
	Semglee vs. Lantus-EU	84	0.98	0.92 - 1.05
	Semglee vs. Lantus-US	78	1.00	0.93 - 1.06

Abbreviations: $AUC_{0-0-30h}$:area under the plasma insulin concentration curve from 0 to 30 hours; $C_{ins.max}$, maximum observed insulin concentration; CI, confidence interval; PK, pharmacokinetics; T/R, test to reference ratio.

Parametric Analysis of Primary and Secondary PD Parameters (PD Analysis Set)

Parameter	Products	Nª	Geometric mean ratio (T/R)	90% CI
Primary PK parameters				
$AUC_{GIR,0-30h}$ [mg/kg]	Lantus (EU) vs. Lantus (US)	104	0.97	0.85 - 1.11
	Semglee vs. Lantus (EU)	104	0.97	0.85 - 1.11
	Semglee vs. Lantus (US)	103	0.94	0.82 - 1.07
GIR_{max} [mg/kg/min]	Lantus (EU) vs. Lantus (US)	102	0.98	0.90 - 1.07
	Semglee vs. Lantus (EU)	103	1.01	0.92 - 1.10
	Semglee vs. Lantus (US)	102	0.99	0.91 - 1.08

Abbreviations: $AUC_{GIR,0-30h}$, area under the glucose infusion rate curve from 0 to 30 hours; CI, confidence interval; GIR_{max}, maximum glucose infusion rate; PD, pharmacodynamic; T/R, test to reference ratio.

Overall, the results established the PK and PD equivalence of Semglee and Lantus-US. The study also demonstrated the PK and PD equivalence of Lantus-US and Lantus-EU.

Immunogenicity Comparison

In study 1 and study 2, the immunogenicity profiles were comparable between Semglee and Lantus-US treatment groups. No clinically relevant differences were seen for percent specific binding response (%SB) for anti-drug antibodies (ADA) or cross-reactive insulin antibody at any post baseline visits. The incidences of total ADA and cross reactive insulin antibody were also comparable between the two treatment groups. No clinically relevant differences were found at any post baseline visits.

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

- Posology

Semglee™ contains insulin glargine, an insulin analogue, and has a prolonged duration of action.

Semglee™ should be administered once daily at any time but at the same time each day.

The pre-filled pen delivers insulin in increments of 1 unit up to a maximum single dose of 80 units.

The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Semglee™ can also be given together with orally active antidiabetic medicinal products. The potency of this medicinal product is stated in units. These units are exclusive to insulin glargine and are not the same as IU or the units used to express the potency of other insulin analogues.

Special population

Elderly population (≥ 65 years old)

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

Renal impairment

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

Hepatic impairment

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

Children

In children, efficacy and safety of Semglee have only been demonstrated when given in the evening.

Due to limited experience, the efficacy and safety of Semglee have not been demonstrated in children below the age of 6 years.

Switch from other insulins to Semglee™

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Semglee™, a change of the dose of the basal insulin may be 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 medicinal products).

Switch from twice daily NPH insulin to Semglee™

To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Semglee™ should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment.

Switch from insulin glargine 300 units/ml to Semglee™

Semglee™ and insulin glargine 300 units/ml are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily insulin glargine 300 units/ml to a once daily regimen with Semglee™ should reduce their dose by approximately 20%.

During the first weeks the reduction should, at least partially, be compensated by an increase in mealtime insulin, after this period the regimen should be adjusted individually.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dose regimen may become necessary. Dose adjustment may also be required, for example, if the patient's weight or life-style changes, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (see section "special warnings and precautions for use"). Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Semglee™.

- **Method of administration**

Semglee™ is administered subcutaneously.

Semglee™ should not be administered intravenously. The prolonged duration of action of Semglee™ is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of Semglee™. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section Special warnings and precautions for use and Undesirable effects).

Semglee™ must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section "List of Excipients".

Special warnings and precautions for use

Due to limited experience, the efficacy and safety of Semglee could not be assessed in children below 6 years of age, in patients with impaired liver function or in patients with moderate / severe renal impairment (see section "Posology and method of administration.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Warnings

Semglee™ is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.

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

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

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. Due to more sustained basal insulin supply with Semglee™, less nocturnal but more early morning hypoglycaemia can be expected.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom 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 aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- 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 (see section "Interaction with other medicinal products and other forms of interaction").

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 insulin glargine may delay recovery from hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area. Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered,
- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section "Interaction with other medicinal products and other forms of interaction").

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia (see section "pharmacodynamic properties").

Handling of the pen

Before using Semglee™ pen, the instructions for use included in the patient information leaflet / instruction for use leaflet must be read carefully. Semglee™ pen has to be used as recommended in these instructions for use (see section "Special precautions for disposal and other handling").

Medication errors

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

Combination of Semglee™ with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Semglee™ is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema.

Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction

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

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (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, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors.

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 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.

Fertility, pregnancy and lactation

Pregnancy

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity.

The use of Semglee™ may be considered 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 hyperglycemia. 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.

Breast-feeding

It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine as a peptide is digested into aminoacids in the human gastrointestinal tract. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate direct harmful effects with respect to fertility.

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 using machines).

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. It should be considered whether it is advisable to drive or use machines in these circumstances.

Undesirable effects

Summary of the safety profile

Hypoglycaemia (very common), 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 (see section "Special warnings and precautions for use").

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare	not known
Immune system disorders				Allergic reactions		
Metabolism and nutrition disorders	Hypoglycaemia					
Nervous system disorders					Dysgeusia	
Eyes disorders				Visual impairment Retinopathy		
Skin and subcutaneous tissue disorders		Lipohypertrophy	Lipoatrophy			Cutaneous amyloidosis
Musculoskeletal and connective tissue disorders					Myalgia	
General disorders and administration site conditions	Injection site reactions			Oedema		

Description of selected adverse reactions

Metabolism and nutrition disorders

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 neuroglycopenia 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 (see section "Special warnings and precautions for use").

Immune system disorders

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

Eyes disorders

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

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section Special warnings and precautions for use).

General disorders and administration site conditions

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

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

Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, 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.

PHARMACEUTICAL PARTICULARS

List of excipients

- Zinc chloride
- Metacresol
- Glycerol
- Hydrochloric acid (for pH adjustment)
- Sodium hydroxide (for pH adjustment)
- Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf life

24 months

Shelf-life after first use of the pen

The medicinal product may be stored for a maximum of 4 weeks not above 30°C and away from direct heat or direct light. Pens in use must not be stored in the refrigerator.

The pen cap must be put back on the pen after each injection in order to protect from light.

Special precautions for storage

Not in-use pens

Store in a refrigerator (2°C-8°C).

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens

For storage conditions after first opening of may be stored for a maximum of 4 weeks not above 30°C and away from direct heat or direct light. Pens in use must not be stored in the refrigerator.

The pen cap must be put back on the pen after each injection in order to protect from light.

Do not leave the needle attached to the pen during storage or reuse needles.

Keep your pen and needles out of sight and reach of children.

Nature and contents of container

Type I colourless glass cartridge with a plunger (bromobutyl rubber), sealed using lined seals (laminate of polyisoprene and bromobutyl rubber). The cartridge is assembled in a disposable pen injector.

Each pre-filled pen contains 3 ml of solution

Packs of 1, 3, 5, 10 pens.

Not all pack sizes may be marketed.

Needles are not included in the pack.

Special precautions for disposal and other handling

Before first use, the pen must be stored at room temperature for 1 to 2 hours.

Inspect the 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. Since Semglee™ is a solution, it does not require resuspension before use.

Semglee™ must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Empty pens must never be reused and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins (see "Special warnings and precautions for use").

Before using Semglee™ pre-filled pen, the instructions for use included in the package leaflet must be read carefully.

The needle sizes compatible with this pen are:
- 31G, 5 mm,
- 32G, 4-6 mm,
- 34G, 4 mm.

Name and address of the manufacturer(s) of the biological active substance(s)

BIOCON SDN. BHD.
No.1, Jalan Bioteknologi 1,
Kawasan Perindustrian SILC 79200 Iskandar Puteri
JOHOR MALAYSIA

Name and address of the manufacturer(s) responsible for batch release

Biocon Biologics Limited,
Block No. B1, B2, B3, Q13 of Q1 and W20 & Unit S18,
1st Floor, Block B4, Special Economic Zone
Plot No. 2, 3, 4 & 5, Phase IV,
Bommasandra - Jigani Link Road,
Bommasandra Post, Bengaluru 560 099, India

™Trademark owned by Mylan

Leaflet revised June 2022

Mylan

Semglee™ insulin glargine injection 100 units/mL (U-100)

BM/0246/01

Semglee™ insulin glargine injection 100 units/mL (U-100)