ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Semglee 100 units/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 units insulin glargine* (equivalent to 3.64 mg).

Each pen contains 3 ml of 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 section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology
Semglee contains insulin glargine, an insulin analogue, and has a prolonged duration of action.
It 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 Semglee and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

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.

Paediatric population
- Adolescents and children aged 2 years and older patients

Safety and efficacy of Semglee have been established in adolescents and children aged 2 years and older (see section 5.1). The dose regimen (dose and timing) should be individually adjusted.
- Children below 2 years of age

The safety and efficacy of Semglee have not been established. No data are available.

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 4.4).

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.

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.

Before using the pre-filled pen, the instructions for use included in the package leaflet must be read carefully (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 4.5).

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,
- 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 4.5).

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 5.1).

Handling of the pen

Before using Semglee pen, the instructions for use included in the package leaflet must be read carefully.
Semglee pen has to be used as recommended in these instructions for use (see section 6.6).

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’.

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 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.

4.6 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.

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 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.

4.8 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 4.4).

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**
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		
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 4.4).

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 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.

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.

Paediatric population

In general, the safety profile for children and adolescents (≤ 18 years of age) is similar to the safety profile for adults.
The adverse reaction 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 children and adolescents (≤ 18 years of age) than in adults.
Clinical study safety data are not available for children under 2 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Semglee is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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 5.2).

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

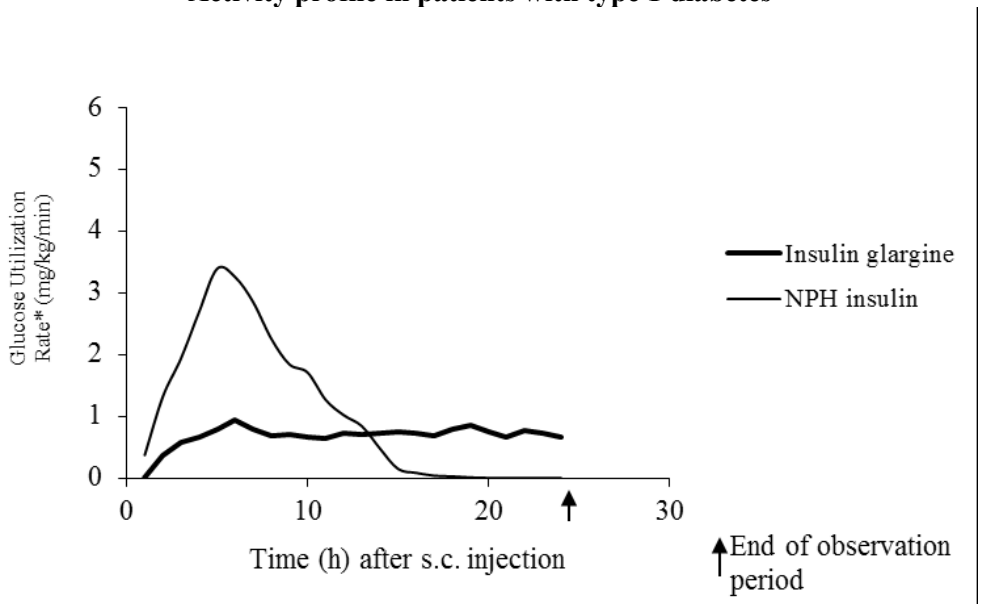
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis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

Activity profile in patients with type 1 diabetes



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

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 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.

5.2 Pharmacokinetic 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 time profile 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 Semglee 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-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of Semglee.
The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Semglee 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 Semglee.

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 5.1). 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

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.

6.4 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 this medicinal product, see section 6.3.

6.5 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.

6.6 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 section 4.4).

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.

7. MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117 allée des Parcs
69800 Saint-Priest
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1270/001
EU/1/18/1270/002
EU/1/18/1270/003
EU/1/18/1270/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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 NUSAJAYA, JOHOR
MALAYSIA

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

McDermott Laboratories t/a Mylan Dublin Biologics
Newenham Court
Northern Cross
Malahide Road
Dublin
17
IRELAND

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Semglee 100 units/ml solution for injection in pre-filled pen
insulin glargine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 units (3.64 mg) insulin glargine

3. LIST OF EXCIPIENTS

Excipients: zinc chloride, metacresol, glycerol, hydrochloric acid and sodium hydroxide (for pH adjustment), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pen of 3 ml
3 pens of 3 ml
5 pens of 3 ml
10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.
Only use needles that are compatible for use with this pre-filled pen.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Not in-use pens
Store in a refrigerator.
Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use conditions
Store below 30°C. Do not refrigerate. Keep the pen cap on the pen after each injection in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117 allée des Parcs
69800 Saint-Priest
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1270/001
EU/1/18/1270/002
EU/1/18/1270/003
EU/1/18/1270/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Semglee

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Semglee 100 units/ml solution for injection
insulin glargine
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Semglee 100 units/ml solution for injection in pre-filled pen
insulin glargine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Semglee is and what it is used for

Semglee contains insulin glargine. This is a modified insulin, very similar to human insulin.

Semglee is used to treat diabetes mellitus in adults, adolescents and children aged 2 years and above. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insulin glargine has a long and steady blood-sugar-lowering action.

2. What you need to know before you use Semglee

Do not use Semglee

- if you are allergic to insulin glargine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Semglee.
Follow closely the instructions for posology, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,

- supplies of insulin, syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require a lot of care (for example, adjustment to insulin dose, blood and urine tests):
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone (oral anti-diabetic medicine used to treat type 2 diabetes mellitus) and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Children

There is no experience with the use of Semglee in children below the age of 2 years.

Other medicines and Semglee

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as acetylsalicylic acid, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),

- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- atypical antipsychotic medicines (such as clozapine, olanzapine),
- protease inhibitors (used to treat HIV).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Semglee with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Semglee contains sodium

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

3. How to use Semglee

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Although Semglee contains the same active substance as insulin glargine 300 units/ml, these medicines are not interchangeable. The switch from one insulin therapy to another requires medical prescription, medical supervision and blood glucose monitoring. Please, consult your doctor for further information.

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will
- determine how much Semglee per day you will need and at what time,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Semglee.

Semglee is a long-acting insulin. Your doctor may tell you to use it in combination with a short-acting insulin or with tablets used to treat high blood sugar levels.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Use in children and adolescents

Semglee can be used in adolescents and children aged 2 years and above. Use this medicine exactly as your doctor has told you.

Frequency of administration

You need one injection of Semglee every day, at the same time of the day.
Semglee pen delivers insulin in increments of 1 unit up to a maximum single dose of 80 units.

Method of administration

Semglee is injected under the skin. Do NOT inject Semglee in a vein, since this will change its action and may cause hypoglycaemia.

Your doctor will show you in which area of the skin you should inject Semglee. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle Semglee pen

Read carefully the "Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new needle must be attached before each use. Only use needles that are compatible with Semglee pen (see “Instructions for Use”).
A safety test must be performed before each injection.

Look at the cartridge before you use the pen. Do not use Semglee if you notice particles in the solution. Only use Semglee if the solution is clear and colourless. Do not shake or mix it before use.

To prevent the possible transmission of disease, never share your pen with anyone else. This pen is only for your use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with Semglee pen, consult your doctor, pharmacist or nurse.

Empty pens must not be re-filled and must be properly discarded.

Do not use Semglee pen if it is damaged or not working properly (due to mechanical defects), it has to be discarded and a new Semglee pen has to be used.

Insulin mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Semglee and other insulins.

If you use more Semglee than you should

If you **have injected too much Semglee**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Semglee

If you have missed a dose of Semglee or if you have not injected enough insulin, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

Do not take a double dose to make up for a forgotten dose.

If you stop using Semglee

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Semglee without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice signs of your blood sugar being too low (hypoglycaemia), take action to increase your blood sugar level straight away (see the box at the end of this leaflet). Hypoglycaemia (low blood sugar) can be very serious and is very common with insulin treatment (may affect more than 1 in 10 people). Low blood sugar means that there is not enough sugar in your blood. If your blood sugar level falls too low you may pass out (become unconscious). Serious hypoglycaemia may cause brain damage and may be life-threatening. For more information, see the box at the end of this leaflet.

Severe allergic reactions (rare, may affect up to 1 in 1,000 people) – the signs may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe allergic reactions to insulins may become life-threatening. Tell a doctor straight away if you notice signs of severe allergic reaction.

Common reported side effects (may affect up to 1 in 10 people)
- **Skin changes at the injection site**

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy, may affect up to 1 in 100 people) or thicken (lipohypertrophy). The insulin may not work very well. Change the injection site with each injection to help prevent these skin changes.
- **Skin and allergic reactions at the injection site**

The signs may include reddening, unusually intense pain when injecting, itching, hives, swelling or inflammation. This can spread around the injection site. Most minor reactions to insulins usually disappear in a few days to a few weeks.

Rare reported side effect (may affect up to 1 in 1,000 people)
- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- **General disorders**

In rare cases, insulin treatment may also cause temporary build-up of water in the body, with swelling in the calves and ankles.

Very rare reported side effects (may affect up to 1 in 10,000 people)
In very rare cases, dysgeusia (taste disorders) and myalgia (muscular pain) can occur.

Use in children and adolescents
In general, the side effects in children and adolescents of 18 years of age or less are similar to those seen in adults.
Complaints of injection site reactions (injection site reaction, injection site pain) and skin reactions (rash, urticaria) are reported relatively more frequently in children and adolescents of 18 years of age or less than in adults.
There is no experience in children under 2 years.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Semglee

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C-8°C). Do not freeze or place next to the freezer compartment of your refrigerator or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in use or carried as a spare may be stored for a maximum of 4 weeks not above 30°C and away from direct heat or direct light. Do not use it after this time period. The pen in use must not be stored in a refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

Remove the needle after the injection and store the pen without the needle. Also, be sure to remove the needle before disposing of the pen. Needles must not be re-used.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Semglee contains

- The active substance is insulin glargine. Each ml of the solution contains 100 units of insulin glargine (equivalent to 3.64 mg).
- The other ingredients are: zinc chloride, metacresol, glycerol, sodium hydroxide (for pH adjustment) (see section 2 “Semglee contains sodium”), hydrochloric acid (for pH adjustment) and water for injections.

What Semglee looks like and contents of the pack

Semglee 100 units/ml solution for injection in a pre-filled pen is a clear colourless solution.
Each pen contains 3 ml of solution for injection (equivalent to 300 units).
Pack sizes of 1, 3, 5, 10 pens.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Mylan S.A.S.
117 allée des Parcs
69800 Saint-Priest
France

Manufacturer

McDermott Laboratories T/A Mylan Dublin Biologics
Newenham Court, Northern Cross, Malahide Road
17 Dublin
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Mylan bvba/sprl
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България
Майлан ЕООД
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Deutschland
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(Sverige)

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Polska
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România
A&G Med Trading SRL
Tel: + 4021 332 49 91

Slovenija
GSP Proizvodi d.o.o.
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Slovenská republika
Mylan s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland
Mylan OY
Puh/Tel: + 358 20 720 9555

Sverige
Mylan AB
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Latvija	**United Kingdom**
BGP Products SIA	Generics [UK] Ltd
Tel: +371 676 055 80	Tel: +44 1707 853000

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Semglee").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Semglee").

Hypoglycaemia is also more likely to occur if
- you have just begun insulin treatment or changed to another insulin preparation (when changing from your previous basal insulin to Semglee hypoglycaemia, if it occurs, may be more likely to occur in the morning than at night),
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Semglee,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Semglee").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
   The recovery of hypoglycaemia may be delayed because Semglee has a long action.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Semglee 100 units/ml solution for injection in pre-filled pen.

INSTRUCTION FOR USE

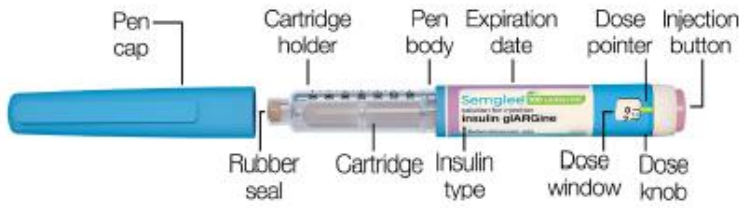
Read these Instructions for Use as well as the package leaflet carefully before using Semglee pre-filled pen and each time you get another pen. There may be new information. This information does not take the place of talking to your doctor, nurse, or pharmacist about your medical condition or your treatment. If you are unable to read or follow all of the instructions on your own, ask for help from someone trained to use this pen. **This pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the pen.**

If you do not follow these instructions each time you use the pen, you may either get too much or too little insulin. This may affect your blood sugar level.

Semglee is a pre-filled disposable pen injector containing 300 units of insulin glargine in 3 mL of solution (100 units/mL). You can inject 1 to 80 units in a single injection.

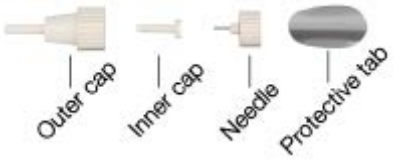
Do not share your Semglee pre-filled pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Pen assembly:



Needles to be obtained separately:
Needle sizes compatible with this pen:

- 31G, 5 mm
- 32G, 4-6 mm
- 34G, 4 mm



Required supplies:
Make sure you have the following items before injecting your dose:

- Semglee pen
- Sterile disposable hypodermic needle compatible with this pen
- 2 alcohol wipes
- Sharps disposal container

Storage
Before first using the pen, store the cartons containing the pen in the refrigerator (2°C-8°C).
Do not freeze the pen.
After you take a pen out of the refrigerator, rest it on a flat surface and wait for it to reach room temperature between 15°C to 30°C before you use it.
After first use of the pen, store it at room temperature up to 30°C. Do not put the pen back in the refrigerator after using it.
Always store the pen with the cap on, to prevent contamination.
The pen that you are using should be thrown away after 4 weeks of first use, even if it still has insulin left in it. See Step 8 for instructions on disposal.
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.
Always use a new sterile needle for each injection as this helps stop blocked needles and prevents infections.

Each time you use the pen

• Wash your hands with soap and water before using your pen.

• Check the pen label to make sure that you are taking the correct type of insulin. The pen has a purple and white label and a purple injection button.

• Check the expiration date on the pen label. **Do not** use the pen after the expiration date.

• Check that the medicine in the pen cartridge looks clear and colourless. **Do not** use the pen if the medicine in the cartridge looks cloudy, coloured or if you can see particles.

• Always use a new sterile disposable needle for each injection.

• Use an injection site that your healthcare provider has shown you.

Step 1. Prepare your pen

A - Inspect the pen: check the purple and white label on the pen to make sure:

• It is the correct insulin type.
• The expiration date has not passed.

B - Hold the pen body with one hand. With the other hand pull off the pen cap. Put the pen cap aside to be used later.

C - Check the insulin through the cartridge holder to make sure:
• The insulin looks clear and colourless.
• There are no cracks, breaks or leaks around the cartridge holder

D - Wipe the rubber seal (at the front of the cartridge) with a new alcohol wipe.

Step 2. Attach a new needle

A - Take a new sterile disposable needle and peel off the protective seal. **Do not** use the needle if the protective seal is damaged or missing as the needle may not be sterile.

B - While holding the pen body facing upwards, attach the outer needle cap straight on to the cartridge holder as shown. Trying to attach the outer needle cap sideways may bend or damage the needle.

C - Turn the outer needle cap in a clockwise (right) direction until it feels tightly fixed on the pen.

D - Carefully pull off the outer needle cap and put it aside. **Do not** throw it away. You will need the outer needle cap later.

E - Carefully pull off the inner needle cap and throw it away.

Step 3. Prime your pen needle

A - Always prime a new pen needle before each injection.

B - Turn the white dose knob to 2 dose units. You will hear a “click” for each unit turned.

If you accidentally turn past 2 units, turn back the dose knob in the opposite direction to the correct number of units.

C - Hold the pen body facing upwards with one hand.

D - Tap the cartridge gently with your finger to help any large air bubbles to move to the top of the cartridge. Small bubbles may still be visible. This is normal.

E - With the pen upright, press the injection button in until it stops moving and the dose window shows “0”.

F - Repeat steps 3B through 3E up to three more times until you see drops of insulin at the tip of the needle.

Priming is complete when you can see drops of insulin.

If you do not see any insulin at the needle tip after 4 priming attempts the needle may be clogged. If this occurs:

• Go to Step 7 for instructions on safely removing the needle.

• Restart the process at step 2A to attach and prime a new needle.

Step 4. Select your dose

A - Check that the dose window shows “0”.

B - Turn the white dose knob until the yellow dose pointer lines up with your required dose.

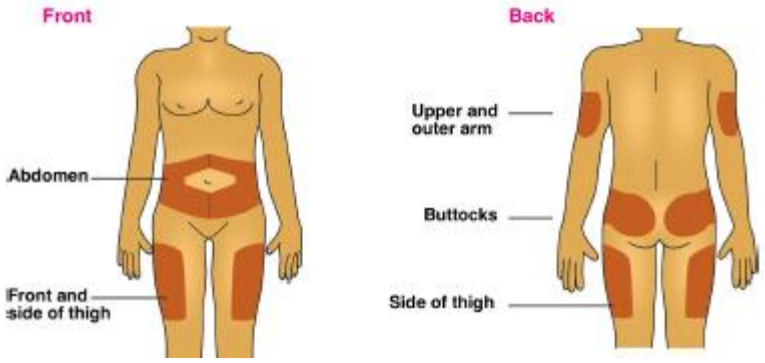
As you turn the white dose knob to set your dose, it will extend out and you will hear a “click” at each unit dialled.

The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the yellow dose pointer.

The pen will not let you dial a dose more than the number of units left in the pen. If your dose is more than the number of units left in the pen, either:
• Inject the amount left in your pen and use a new pen to give the rest of your dose,
or
• Get a new pen and inject the full dose.

Do not force the dose knob to turn beyond 80 units.
Do not push the purple injection button when turning the dose knob.

Step 5. Select and clean the injection site
A - Select the injection site as explained to you by your healthcare provider, clean with a new alcohol wipe and let your skin dry before you inject your dose.
Injection sites include your arms, thighs, buttocks and abdomen. You should change your injection site for each injection.



Step 6. Inject your dose
A - If instructed by your healthcare provider you can pinch the cleaned skin between your fingers.

B - Push the needle straight into the skin as shown by your healthcare provider.
Do not inject with the needle at an angle.

C - Press the purple injection button all the way in. The white dose knob will turn and you will hear "clicks" as you press down.

D - Hold the purple injection button down for 10 seconds after the dose window shows “0” to make sure all of the insulin is injected. If you do not keep the injection button pressed down for 10 seconds after “0” is displayed you may get the wrong dose of medicine.

Do not push the injection button sideways or block the white dose knob with your fingers as this will stop you from injecting the medicine.

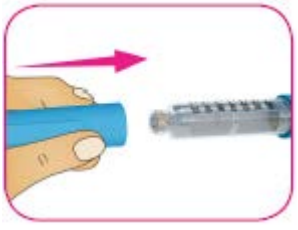
Step 7. After your injection

A - Take the outer needle cap that you had saved in step 2D, hold it at the widest part and carefully cover the needle without touching it.

B - Squeeze the wide part of the outer needle cap and unscrew the needle in an anti-clockwise (left) direction. Keep twisting the needle until it comes off the pen. It may take several twists to release the needle.

C - Put the needle in a sharps disposal container (see Step 8 for instructions on disposal)

D - Replace the pen cap over the cartridge.



E - Store the pen at room temperature (under 30°C). **Do not** store the pen with a used needle attached.

Step 8. Disposal
Put your used needle in a sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles in your household waste.
If you do not have a sharps container, you may use a household container that is:
• made of heavy duty plastic,
• can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
• upright and stable during use,
• leak-resistant, and
• properly labelled to warn of hazardous waste inside the container.

The used pen may be discarded in your household waste after you have removed the needle.

Pen care
• Always carry an extra insulin pre-filled pen injector as recommended by your healthcare provider in case your pen gets lost or damaged.
• Always use a new sterile disposable needle for each injection.
• Keep your pen away from moisture, dust, direct sunlight and places where the temperature may get too high or low (see storage section at the beginning of these instructions)
• You can clean the outside of your pen by wiping it with a damp cloth.
• Avoid dropping your pen as this can cause the cartridge to break, or can damage the pen.
• **Do not** share your pen with other people, even if the needle has been changed. You may give other people serious infection or get a serious infection from them.
• **Do not** soak or wash your pen. **Do not** use alcohol, hydrogen peroxide, bleach, or any other liquids to clean your pen. **Do not** apply lubricants such as oil. This could damage the pen.
• **Do not** try to fix an unusable or damaged pen. Remove the needle as described in Step 7, and discard the pen or return it to the pharmacist. Use a new pen instead.