1. NAME OF THE MEDICINAL PRODUCT

Suliqua 100/50 solution for injection in a pre-filled pen
Suliqua 100/33 solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Suliqua 100 units/ml + 50 microgram/ml solution for injection in pre-filled pen
Each pre-filled pen contains 300 units of insulin glargine* and 150 micrograms lixisenatide in 3 ml solution.
Each ml contains 100 units of insulin glargine and 50 micrograms of lixisenatide.
Each dose step contains 1 unit of insulin glargine and 0.5 micrograms of lixisenatide

Suliqua 100units/ml + 33 microgram/ml solution for injection in pre-filled pen
Each pre-filled pen contains 300 units of insulin glargine and 100 micrograms of lixisenatide in 3 ml solution.
Each ml contains 100 units of insulin glargine and 33 micrograms of lixisenatide.
Each dose step contains 1 unit of insulin glargine and 0.33 micrograms of lixisenatide

*Insulin glargine is produced by recombinant DNA technology in *Escherichia coli*.

The dose window on the pen shows the number of dose steps.

Excipient(s) with known effects:
Each ml contains 2.7 milligrams of metacresol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (SoloStar)

Clear colourless solution.

Patient safety information Card
The marketing of SULIQUA is subject to a risk management plan (RMP) including a 'Patient information card'.
The 'Patient information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Suliqua is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin (see section 4.4 and 5.1 for available data on the different combinations).

4.2 Posology and method of administration

Suliqua is available in two pre-filled pens, providing different dosing options, i.e. Suliqua (10-40) pen, Suliqua (30-60) pen respectively. The differentiation between the pen strengths is based on the dose range of the pen.

- Suliqua 100 units/ml + 50 micrograms/ml pre-filled pen delivers dose steps from **10-40 units** of insulin glargine in combination with **5-20 mcg** of lixisenatide (Suliqua (10-40) pen).
- Suliqua 100 units/ml + 33 micrograms/ml pre-filled pen delivers dose steps from **30-60 units** of insulin glargine in combination with **10-20 mcg** of lixisenatide (Suliqua (30-60) pen).

To avoid medication errors, the prescriber must make sure that the correct strength and number of dose steps is stated in the prescription (see section 4.4).

Posology

The dose must be individualised based on clinical response and is titrated based on the patient's need for insulin. The lixisenatide dose is increased or decreased along with insulin glargine dose and also depends on which pen is used.

Starting dose

Therapy with basal insulin or oral glucose lowering medicinal product other than metformin should be discontinued prior to initiation of Suliqua.

The starting dose of Suliqua is based on previous anti-diabetic treatment, and in order not to exceed the recommended lixisenatide starting dose of 10 mcg:

		Previous therapy		
		Oral anti-diabetic treatment (insulin naïve patients)	**Insulin glargine (100 units/ml)** ≥20 to <30 units**	**Insulin glargine (100 units/ml)** ≥30 to ≤60 units**
Starting dose and pen	**Suliqua (10-40) pen**	10 dose steps (10 units/5 mcg)*	20 dose steps (20 units/10 mcg)*	
	Suliqua (30-60) pen			30 dose steps (30 units/10 mcg)*

* Units insulin glargine (100 units/ml) / mcg lixisenatide

**** If a different basal insulin was used:**

- For twice daily basal insulin or insulin glargine (300 units/ml), the total daily dose previously used should be reduced by 20% to choose the Suliqua starting dose.
- For any other basal insulin the same rule as for insulin glargine (100 units/ml) should be applied

The maximum daily dose is 60 units insulin glargine and 20 mcg lixisenatide corresponding to 60 dose steps.

Suliqua should be injected once a day within one hour prior to a meal. It is preferable that the prandial injection is performed before the same meal every day, when the most convenient meal has been chosen.

Dose titration

Suliqua is to be dosed in accordance with the individual patient's need for insulin. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose (see section 5.1). Close glucose monitoring is recommended during the transfer and in the following weeks.

- If the patient starts with the Suliqua (10-40) pen, the dose may be titrated up to 40 dose steps with this pen.
- For doses >40 dose steps/day titration must be continued with Suliqua (30-60) pen.
- If the patient starts with the Suliqua (30-60) pen, the dose may be titrated up to 60 dose steps with this pen.
- For total daily doses >60 dose steps/day, Suliqua must not be used.

Patients adjusting the amount or timing of dosing should only do so under medical supervision with appropriate glucose monitoring (see section 4.4).

Special population

Elderly (≥65 years old)
Suliqua can be used in elderly patients. The dose should be adjusted on an individual basis, based on glucose monitoring. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. For lixisenatide no dose adjustment is required based on age. The therapeutic experience of Suliqua in patients ≥75 years of age is limited.

Renal impairment
Suliqua is not recommended in patients with severe renal impairment and end-stage renal disease as there is no sufficient therapeutic experience with use of lixisenatide.
No dose adjustment is required for lixisenatide in patients with mild or moderate renal impairment. In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.
In patients with mild to moderate renal impairment using Suliqua, frequent glucose monitoring and dose adjustment may be necessary.

Hepatic impairment
No dose adjustment of lixisenatide is needed in patients with hepatic impairment (see section 5.2). In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. Frequent glucose monitoring and dose adjustment may be necessary for Suliqua in patients with hepatic impairment.

Paediatric population
There is no relevant use of Suliqua in the paediatric population.

Method of administration

Suliqua is to be injected subcutaneously in the abdomen, deltoid, or thigh.

The injection sites should be rotated within the same region (abdomen, deltoid, or thigh) from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the Instructions for Use accompanying the package leaflet (see section 6.6).

Suliqua must not be drawn from the cartridge of the pre-filled pen into a syringe to avoid dosing errors

and potential overdose (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substances 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 of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Type 1 diabetes mellitus

Suliqua should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Rotation of the injection site

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 medicinal product may be considered.

Hypoglycaemia

Hypoglycaemia was the most frequently reported observed adverse reaction during treatment with Suliqua (see section 4.8). Hypoglycaemia may occur if the dose of Suliqua is higher than required.

Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These factors 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).
- lixisenatide and/or insulin in combination with a sulfonylurea may result in an increased risk of hypoglycaemia. Therefore Suliqua should not be given in combination with a sulfonylurea.

The dose of Suliqua must be individualised based on clinical response and is titrated based on the patient's need for insulin (see section 4.2).

Acute pancreatitis

Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with lixisenatide although a causal relationship has not been established. Patients should be informed of

the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Suliqua should be discontinued; if acute pancreatitis is confirmed, lixisenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Severe gastrointestinal disease

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions (see section 4.8). Suliqua has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis and therefore, the use of Suliqua is not recommended in these patients.

Severe renal impairment

There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease. Use is not recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Concomitant medicinal products

The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Suliqua should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products are given in section 4.5.

Dehydration

Patients treated with Suliqua should be advised of the potential risk of dehydration in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Antibody formation

Administration of Suliqua may cause formation of antibodies against insulin glargine and/or lixisenatide. In rare cases, the presence of such antibodies may necessitate adjustment of the Suliqua dose in order to correct a tendency for hyperglycaemia or hypoglycaemia.

Avoidance of medication errors

Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between the two different strengths of Suliqua and mix-ups with other injectable diabetes medicinal products.
To avoid dosing errors and potential overdose, neither the patients nor healthcare professionals should ever use a syringe to draw the medicinal product from the cartridge in the pre-filled pen into a syringe.

Antidiabetic medicinal products not studied in combination with Suliqua

Suliqua has not been studied in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, glinides, and pioglitazone

Travel

To avoid dosing errors and potential overdoses with changing to different time zones, the patient should seek the doctor’s advice before travelling.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicinal product contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with Suliqua have been performed. The information given below is based on studies with the monocomponents.

Pharmacodynamic interactions

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

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include anti-hyperglycaemic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide 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.

Pharmacokinetic interactions

Lixisenatide is a peptide and is not metabolised by cytochrome P450. In *in vitro* studies, lixisenatide did not affect the activity of cytochrome P450 isozymes or human transporters tested.
No pharmacokinetic interactions are known for insulin glargine.

Effect of gastric emptying on oral medicinal products
The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely, especially at the time of initiation of lixisenatide treatment. These medicinal products should be taken in a standardised way in relation to lixisenatide. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when lixisenatide is not administered.

For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before or 4 hours after lixisenatide injection.

Gastro-resistant formulations containing substances sensitive to stomach degradation, should be administered 1 hour before or 4 hours after lixisenatide injection.

Paracetamol
Paracetamol was used as a model medicinal product to evaluate the effect of lixisenatide on gastric emptying. Following administration of a single dose of paracetamol 1000 mg, paracetamol AUC and $t_{1/2}$ were unchanged whatever the timing of its administration (before or after the lixisenatide injection). When administered 1 or 4 hours after 10 mcg lixisenatide, C_{max} of paracetamol was decreased by 29% and 31%, respectively and median t_{max} was delayed by 2.0 and 1.75 hours,

respectively. A further delay in t_{max} and a reduced C_{max} of paracetamol have been predicted with the 20 mcg maintenance dose.
No effects on paracetamol C_{max} and t_{max} were observed when paracetamol was administered 1 hour before lixisenatide.

Based on these results, no dose adjustment for paracetamol is required but the delayed t_{max} observed when paracetamol is administered 1-4 hours after lixisenatide should be taken into account when a rapid onset of action is required for efficacy.

Oral contraceptives
Following administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after 10 mcg lixisenatide, the C_{max}, AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel were unchanged.

Administration of the oral contraceptive 1 hour or 4 hours after lixisenatide did not affect AUC and $t_{1/2}$ of ethinylestradiol and levonorgestrel, whereas C_{max} of ethinylestradiol was decreased by 52% and 39%, respectively and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively and median t_{max} was delayed by 1 to 3 hours.
The reduction in C_{max} is of limited clinical relevance and no dose adjustment for oral contraceptives is required.

Atorvastatin
When lixisenatide 20 mcg and atorvastatin 40 mg were co-administered in the morning for 6 days, the exposure to atorvastatin was not affected, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours.

No such increase for t_{max} was observed when atorvastatin was administered in the evening and lixisenatide in the morning but the AUC and C_{max} of atorvastatin were increased by 27% and 66%, respectively.

These changes are not clinically relevant and, therefore, no dose adjustment for atorvastatin is required when co-administered with lixisenatide.

Warfarin and other coumarin derivatives
After concomitant administration of warfarin 25 mg with repeated dosing of lixisenatide 20 mcg, there were no effects on AUC or INR (International Normalised Ratio) while C_{max} was reduced by 19% and t_{max} was delayed by 7 hours.
Based on these results, no dose adjustment for warfarin is required when co-administered with lixisenatide; however, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives is recommended at the time of initiation or ending of lixisenatide treatment.

Digoxin
After concomitant administration of lixisenatide 20 mcg and digoxin 0.25 mg at steady state, the AUC of digoxin was not affected. The t_{max} of digoxin was delayed by 1.5 hour and the C_{max} was reduced by 26%.
Based on these results, no dose adjustment for digoxin is required when co-administered with lixisenatide.

Ramipril
After concomitant administration of lixisenatide 20 mcg and ramipril 5 mg during 6 days, the AUC of ramipril was increased by 21% while the C_{max} was decreased by 63%. The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2.5 hours.
Based on these results, no dose adjustment for ramipril is required when co-administered with lixisenatide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Suliqua is not recommended in women of childbearing potential not using contraception.

Pregnancy

There is no clinical data on exposed pregnancies from controlled clinical studies with use of Suliqua, insulin glargine, or lixisenatide.

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) with insulin glargine indicate no malformative nor feto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity with insulin glargine.
There are no or limited amount of data from the use of lixisenatide in pregnant women. Studies with lixisenatide in animals have shown reproductive toxicity (see section 5.3).
Suliqua is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether insulin glargine or lixisenatide are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Suliqua.

Fertility

Animal studies with lixisenatide or insulin glargine do not indicate direct harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Suliqua has no or negligible influence on the ability to drive or use machines. However, 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 while driving and using machines. 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

The most frequently reported adverse reactions during treatment with Suliqua were hypoglycaemia and gastrointestinal adverse reactions (see section 'Description of selected adverse reactions' below).

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 frequency (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) ; not known: cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency			
	Very common	**Common**	**Uncommon**	**Not Known**
Infections and infestations			Nasopharyngitis Upper respiratory tract infection	
Immune system disorders			Urticaria	
Metabolism and nutrition disorders	Hypoglycaemia			
Nervous system disorders		Dizziness	Headache	
Gastrointestinal disorders		Nausea Diarrhoea Vomiting	Dyspepsia Abdominal pain	
Skin and subcutaneous tissue disorders				Cutaneous amyloidosis Lipodystrophy
General disorders and administration site conditions		Injection site reactions	Fatigue	

Description of selected adverse reactions

Hypoglycaemia
The following table describes the rate of documented symptomatic hypoglycaemia (≤3.9 mmol/L) and severe hypoglycaemia for both Suliqua and the comparator.

Documented symptomatic or severe hypoglycaemic adverse reactions

	Insulin naïve patients			**Switch from basal insulin**	
	Suliqua	**Insulin glargine**	**Lixisenatide**	**Suliqua**	**Insulin glargine**
N	469	467	233	365	365
Documented symptomatic hypoglycaemia*					
Patients with event, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)	146 (40.0%)	155 (42.5%)
Events per patient-year, n	1.44	1.22	0.34	3.03	4.22
Severe hypoglycaemia**					
Events per patient-year, n	0	<0.01	0	0.02	<0.01

* Documented symptomatic hypoglycaemia was an event during which typical symptoms of hypoglycaemia were accompanied by a measured plasma glucose concentration of ≤3.9 mmol/L.
** Severe symptomatic hypoglycaemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Gastrointestinal disorders
Gastrointestinal adverse reactions (nausea, vomiting and diarrhoea) were frequently reported adverse reactions during the treatment period. In patients treated with Suliqua, the incidence of related nausea, diarrhoea and vomiting was 8.4%, 2.2% and 2.2%, respectively. Gastrointestinal adverse reactions were mostly mild and transient in nature.

Immune system disorders
Allergic reactions (urticaria) possibly related with Suliqua have been reported in 0.3% of patients. Cases of generalised allergic reaction including anaphylactic reaction and angioedema have been reported during marketed use of insulin glargine and lixisenatide.

Immunogenicity
Administration of Suliqua may cause formation of antibodies against insulin glargine and/or lixisenatide.

The incidence of formation of anti- insulin glargine antibodies was 21% and 26.2%. In approximately 93% of the patients, anti-insulin glargine antibodies showed cross-reactivity to human insulin. The incidence of formation of anti- lixisenatide antibodies was approximately 43%. Neither status for anti-insulin glargine antibodies nor for anti-lixisenatide antibodies had a clinically relevant impact on safety or efficacy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site of insulins 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 4.4).

Injection site reactions
Some (1.7%) patients using insulin containing therapy, including Suliqua have experienced erythema, local oedema, and pruritus at the site of injection.

Heart rate
Increase in heart rate has been reported with GLP-1receptor agonist use and a transient increase was also observed in some studies with lixisenatide. No increase in mean heart rate was seen in all phase 3 studies with Suliqua.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at *https://sideeffects.health.gov.il/*.

4.9 Overdose

Hypoglycaemia and gastrointestinal adverse reactions may develop if a patient is dosed with more Suliqua than required.

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 of hypoglycaemia 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.

In case of gastrointestinal adverse reactions, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting.
ATC Code: A10AE54.

Mechanism of action

Suliqua combines two active substances with complementary mechanisms of action to improve glycaemic control: insulin glargine, a basal insulin analogue (mainly targeting fasting plasma glucose), and lixisenatide, a GLP-1 receptor agonist (mainly targeting postprandial glucose).

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

Lixisenatide
Lixisenatide is a GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas.
Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved. A postprandial injection of Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose is absorbed and appears in the circulation.

Pharmacodynamic effects

Suliqua
The combination of insulin glargine and lixisenatide has no impact on the pharmacodynamics of insulin glargine. The impact of the combination of insulin glargine and lixisenatide on the pharmacodynamics of lixisenatide has not been studied in phase 1 studies.
Consistent with a relatively constant concentration/time profile of insulin glargine over 24 hours with no pronounced peak when administered alone, the glucose utilisation rate/time profile was similar when given in the insulin glargine/lixisenatide combination.
The time course of action of insulins, including Suliqua, may vary between individuals and within the same individual.

Insulin glargine
In clinical studies with insulin glargine (100 units/ml) the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin.

Lixisenatide
In a 28-day placebo-controlled study in patients with type 2 diabetes 5 to 20 mcg lixisenatide resulted in a statistically significant decreases in postprandial blood glucose after breakfast, lunch and dinner.

Gastric emptying
Following a standardised labelled test meal, in the study referred to above, it was confirmed that lixisenatide slows gastric emptying, thereby reducing the rate of postprandial glucose absorption. The slowing effect of gastric emptying was maintained at the end of the study.

Clinical efficacy and safety

The safety and effectiveness of Suliqua on glycaemic control were evaluated in two randomised clinical studies in patients with type 2 diabetes mellitus:

- Add-on to metformin [Insulin Naïve]
- Switch from basal insulin

In each of the active-controlled clinical studies, treatment with Suliqua produced clinically and statistically significant improvements in hemoglobin A1c (HbA1c).
Reaching lower HbA1c levels and achieving greater HbA1c reduction did not increase rates of hypoglycaemia with combination treatment versus insulin glargine alone (see section 4.8).

In the Add-on to metformin clinical study the treatment was started at 10 dose steps (10 units insulin glargine and 5 mcg lixisenatide). In the switch from basal insulin clinical study the starting dose was 20 dose steps (20 units insulin glargine and 10 mcg lixisenatide) or 30 dose steps, (30 units insulin glargine and 10 mcg lixisenatide), see section 4.2, depending on the previous insulin dose. In both studies the dose was titrated once weekly, based on fasting self-measured plasma glucose values.

Add-on to metformin [insulin naïve]

Clinical study in patients with Type 2 diabetes insufficiently controlled on an oral anti-diabetic (OAD) treatment
A total of 1170 patients with type 2 diabetes were randomised in an open label, 30-week, active-controlled study to evaluate the efficacy and safety of Suliqua compared to the individual components, insulin glargine (100 units/ml) and lixisenatide (20 mcg).

Patients with type 2 diabetes, treated with metformin alone or metformin and a second OAD treatment that could be a sulfonylurea or a glinide or SGLT-2 inhibitor or a dipeptidyl peptidase-4 (DPP-4) inhibitor, and who were not adequately controlled with this treatment (HbA1c range 7.5% to 10% for patients previously treated with metformin alone and 7% to 9% for patients previously treated with

metformin and a second oral anti-diabetic treatment) entered a run-in period for 4 weeks. During this run-in phase metformin treatment was optimised and any other OADs were discontinued. At the end of the run-in period, patients who remained inadequately controlled (HbA1c between 7% and 10%) were randomised to either Suliqua, insulin glargine or lixisenatide. Of the 1479 patients who started the run-in phase, 1170 were randomised. The main reasons for not entering the randomised phase were FPG value >13.9 mmol/L and HbA1c value <7% or >10% at the end of the run-in phase

The randomised type 2 diabetes population had the following characteristics: Mean age was 58.4 years with the majority (57.1%) being aged of 50 to 64 years, and 50.6 percent were male. The mean BMI at baseline was 31.7 kg/m^2 with 63.4% of patients having a BMI ≥30 kg/m^2. The mean duration of diabetes was approximately 9 years. Metformin was a mandatory background therapy and 58% of patients received a second OAD at screening, being a sulfonylurea in 54% of patients.

At week 30, Suliqua provided statistically significant improvement in HbA1c (p-value <0.0001) compared to the individual components. In a pre-specified analysis of this primary endpoint, the differences observed were consistent with regard to baseline HbA1c (<8% or ≥8%) or baseline OAD use (metformin alone or metformin plus second OAD).
See table and figure below for the other endpoints in the study.

Table 3: Results at 30 weeks - Add-on to metformin clinical study (mITT population)

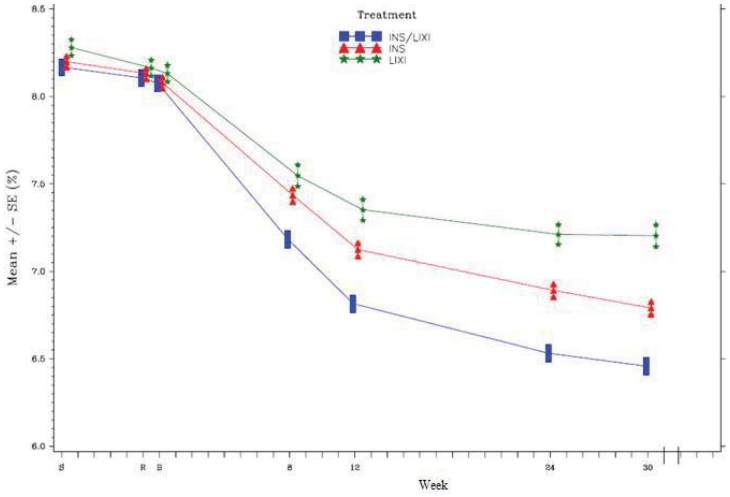
	Suliqua	**Insulin glargine**	**Lixisenatide**
Number of subjects (mITT)	468	466	233
HbA1c (%)			
Baseline (mean; post run-in phase)	8.1	8.1	8.1
End of study (mean)	6.5	6.8	7.3
LS change from baseline (mean)	-1.6	-1.3	-0.9
Difference vs. insulin glargine [95% confidence interval] (p-value)		-0.3 [-0.4, -0.2] (<0.0001)	
Difference vs. lixisenatide [95% confidence interval] (p-value)			-0.8 [-0.9, -0.7] (<0.0001)
Number of Patients (%) reaching HbA1c <7% at week 30*	345 (74%)	277 (59%)	77 (33%)
Fasting plasma glucose (mmol/L)			
Baseline (mean)	9.88	9.75	9.79
End of study (mean)	6.32	6.53	8.27
LS change from baseline (mean)	-3.46	-3.27	-1.50
LS difference versus glargine (mean) [95% confidence interval] (p-value)		-0.19 [-0.420 to 0.038] (0.1017)	
LS difference versus lixisenatide (mean) [95% confidence interval] (p-value)			-1.96 [-2.246 to -1.682] (<0.0001)
2 hour PPG (mmol/L)**			
Baseline (mean)	15.19	14.61	14.72
End of study (mean)	9.15	11.35	9.99
LS change from baseline	-5.68	-3.31	-4.58
LS difference versus glargine (mean)		-2.38	

[95% confidence interval]		(-2.79 to -1.96)	

LS difference versus lixisenatide (mean) [95% confidence interval]			-1.10 (-1.63 to -0.57)
Mean body weight (kg)			
Baseline (mean)	89.4	89.8	90.8
LS change from baseline (mean)	-0.3	1.1	-2.3
Comparison versus insulin glargine [95% confidence interval] (p-value)		-1.4 [-1.9 to -0.9] (<0.0001)	
Comparison versus lixisenatide [95% confidence interval]*			2.01 [1.4 to 2.6]
Number (%) of patients achieving HbA1c <7% with no body weight gain at week 30	202 (43.2%)	117 (25.1%)	65 (27.9%)
Proportion difference vs. insulin glargine [95% confidence interval] (p-value)		18.1 [12.2 to 24.0] (<0.0001)	
Proportion difference vs. lixisenatide [95% confidence interval]*			15.2 [8.1 to 22.4]
Insulin glargine daily dose			
LS insulin dose at week 30 (mean)	39.8	40.5	NA

*Not included in the pre-specified step-down testing procedure
**2 hour PPG minus the pre-meal glucose value

Figure 1: Mean HbA1c(%) by visit during 30-week randomised treatment period - mITT population



Patients in the Suliqua group reported a statistically significantly greater decrease in the average 7-point self-monitored plasma glucose (SMPG) profile from baseline to Week 30 (-3.35 mmol/L) compared to patients in the insulin glargine group (-2.66 mmol/L; difference -0.69 mmol/L) and patients in the lixisenatide group (-1.95 mmol/L; difference -1.40 mmol/L) ($p<0.0001$ for both comparisons). At all time points, 30-week mean plasma glucose values were lower in the Suliqua group than in both the insulin glargine group and the lixisenatide group, with the only exception of the pre-breakfast value which was similar between the Suliqua group and the insulin glargine group.

Switch from basal insulin

Clinical study in patients with Type 2 diabetes insufficiently controlled on basal insulin
A total of 736 patients with type 2 diabetes participated in a randomised, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicentere study to evaluate the efficacy and safety of Suliqua compared to insulin glargine (100 units/ml).

Patients screened had type 2 diabetes were treated with basal insulin for at least 6 months, receiving a stable daily dose of between 15 and 40 U alone or combined with 1 or 2 OADs (metformin or a sulfonylurea or a glinide or a SGLT-2 inhibitor or a DPP-4 inhibitor), had an HbA1c between 7.5% and 10% (mean HbA1c of 8.5% at screening) and a FPG less than or equal to 10.0 mmol/L or 11.1 mmol/L depending on their previous anti-diabetic treatment.

After screening, eligible patients (n=1018) entered a 6 week run-in phase where patients remained on or switched to insulin glargine, in case they took another basal insulin, and had their insulin dose titrated/stabilised while continuing metformin (if previously taken). Any other OADs were discontinued.
At the end of the run-in period, patients with an HbA1c between 7 and 10% , FPG ≤7.77 mmol/L and insulin glargine daily dose of 20 to 50 units, were randomised to either Suliqua (n=367) or insulin glargine (n=369).

This type 2 diabetes population had the following characteristics: mean age was 60.0 years with the majority (56.3%) being aged of 50 to 64 years, and 53.3 percent were female. The mean BMI at baseline was 31.1 kg/m^2 with 57.3% of patients having a BMI ≥30 kg/m^2. The mean diabetes duration was approximately 12 years and the mean duration of previous basal insulin treatment was approximately 3 years. At screening 64.4% of patients were receiving insulin glargine as basal insulin and 95% received at least 1 concomitant OAD.
At week 30, Suliqua provided statistically significant improvement in HbA1c (p-value <0.0001) compared to insulin glargine.
See table and figure below for the other endpoints in the study.

Table 4: Results at 30 weeks -Study Type 2 diabetes uncontrolled on basal insulin mITT population

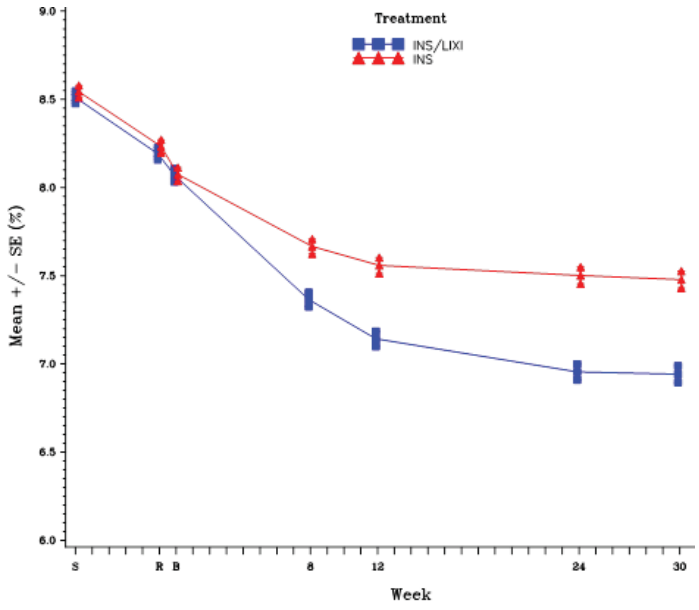
	Suliqua	**Insulin glargine**
Number of subjects (mITT)	366	365
HbA1c (%)		
Baseline (mean; post run-in phase)	8.1	8.1
End of treatment (mean)	6.9	7.5
LS change from baseline (mean)	-1.1	-0.6
Difference versus insulin glargine [95% confidence interval] (p-value)	-0.5 [-0.6, -0.4] (<0.0001)	
Patients [n (%)] reaching HbA1c <7% at week 30*	201 (54.9%)	108 (29.6%)
Fasting plasma glucose (mmol/L)		
Baseline (mean)	7.33	7.32
End of study (mean)	6.78	6.69
LS change from baseline (mean)	-0.35	-0.46
Difference versus insulin glargine [95% confidence interval]	0.11 (-0.21 to 0.43)	
2 hour PPG (mmol/L)**		
Baseline (mean)	14.85	14.97
End of study (mean)	9.91	13.41

LS change from baseline (mean)	-4.72	-1.39
LS difference versus glargine (mean) [95% confidence interval]	-3.33 (-3.89 to -2.77)	
Mean body weight (kg)		
Baseline (mean)	87.8	87.1
LS change from baseline (mean)	-0.7	0.7
Comparison versus insulin glargine [95% confidence interval] (p-value)	-1.4 [-1.8 to -0.9] (<0.0001)	
Number (%) of patients achieving HbA1c< 7.0% with no body weight gain at week 30	125 (34.2%)	49 (13.4%)
Proportion difference versus insulin glargine [95% confidence interval] (p-value)	20.8 [15.0 to 26.7] (<0.0001)	
Insulin glargine daily dose		
Baseline (mean)	35.0	35.2
Endpoint (mean)	46.7	46.7
LS insulin dose change at week 30 (mean)	10.6	10.9

*Not included in the pre-specified step-down testing procedure

**2 hour PPG minus the pre-meal glucose value

Figure 2: Mean HbA1c (%) by visit during 30-week randomised treatment period - mITT population



Cardiovascular outcome studies

The cardiovascular safety of insulin glargine and lixisenatide has been established in the ORIGIN and ELIXA clinical studies, respectively. No dedicated cardiovascular outcome trial has been conducted with Suliqua.

Insulin glargine

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomised, 12,537 patient study that compared insulin glargine 100 Unitsto standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of cardiovascular (CV) death, nonfatal myocardial infarction and nonfatal stroke. The median duration of study follow-up was 6.2 years. The incidence of MACE was similar between insulin glargine 100 Units and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)].

Lixisenatide

The ELIXA study was a randomised, double-blind, placebo-controlled, multinational study that evaluated CV outcomes during treatment with lixisenatide in patients (n=6068) with type 2 diabetes mellitus after a recent Acute Coronary Syndrome. The primary composite efficacy endpoint was the time to the first occurrence of any of the following events: CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. The median duration of study follow-up was 25.8 and 25.7 months in the lixisenatide group and the placebo group, respectively.

The incidence of the primary endpoint was similar in the lixisenatide (13.4%) and placebo (13.2%) groups: the hazard ratio (HR) for lixisenatide versus placebo was 1.017, with an associated 2-sided 95% confidence interval (CI) of 0.886 to 1.168.

5.2 Pharmacokinetic properties

Absorption

The insulin glargine/lixisenatide ratio has no relevant impact on the PK of insulin glargine and lixisenatide in Suliqua.

After subcutaneous administration of insulin glargine/lixisenatide combinations to patients with type 1 diabetes, insulin glargine showed no pronounced peak. Exposure to insulin glargine following administration of the insulin glargine/lixisenatide combination was 86-88 % compared to administration of separate simultaneous injections of insulin glargine and lixisenatide. This difference is not considered clinically relevant.

After subcutaneous administration of insulin glargine/lixisenatide combinations to patients with type 1 diabetes, the median t_{max} of lixisenatide was in the range of 2.5 to 3.0 hours. AUC was comparable while there was a small decrease in C_{max} of lixisenatide of 22-34% compared with separate simultaneous administration of insulin glargine and lixisenatide, which is not likely to be clinically significant.

There are no clinically relevant differences in the rate of absorption when lixisenatide as monotherapy is administered subcutaneously in the abdomen, deltoid, or thigh.

Distribution

The apparent volume of distribution of insulin glargine after subcutaneous administration of the insulin glargine/lixisenatide combinations (Vss/F) is approximately 1700 L.

Lixisenatide has a low level (55%) of binding to human proteins. The apparent volume of distribution of lixisenatide after subcutaneous administration of insulin glargine/lixisenatide combinations (Vz/F) is approximately 100 L.

Biotransformation

A metabolism study in diabetic patients who received insulin glargine alone indicates that insulin glargine is rapidly metabolised at the carboxyl terminus of the B chain to form 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 pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine is principally based on exposure to M1.

As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism.

Elimination

After single subcutaneous administration of the insulin glargine/lixisenatide combination, the mean apparent clearance (CL/F) of insulin glargine was approximately 120 L/h.

After multiple-dose subcutaneous administration of Lixisenatide in patients with type 2 diabetes, mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h.

Special populations

Renal impairment
In subjects with mild (creatinine clearance calculated by the Cockcroft-Gault formula 60-90 ml/min), moderate (creatinine clearance 30-60 ml/min) and severe renal impairment (creatinine clearance 15-30 ml/min) AUC of lixisenatide was increased by 46%, 51% and 87%, respectively.
Insulin glargine has not been studied in patients with renal impairment. In patients with renal impairment, however, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
As lixisenatide is cleared primarily by the kidney, no pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.
Insulin glargine has not been studied in diabetes patients with hepatic impairment. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Age, race, gender and body weight

Insulin glargine
Effect of age, race, and gender on the pharmacokinetics of insulin glargine has not been evaluated. In controlled clinical studiesin adults with insulin glargine (100 units/ml), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy.

Lixisenatide
Age has no clinically relevant effect on the pharmacokinetics of lixisenatide. In a pharmacokinetic study in elderly non-diabetic subjects, administration of lixisenatide 20 mcg resulted in a mean increase of lixisenatide AUC by 29% in the elderly population (11 subjects aged 65 to 74 years and 7 subjects aged ≥75 years) compared to 18 subjects aged 18 to 45 years, likely related to reduced renal function in the older age group.

Ethnic origin had no clinically relevant effect on the pharmacokinetics of lixisenatide based on the results of pharmacokinetic studies in Caucasian, Japanese and Chinese subjects.

Gender has no clinically relevant effect on the pharmacokinetics of lixisenatide

Body weight has no clinically relevant effect on lixisenatide AUC.

Immunogenicity

In the presence of anti-lixisenatide antibodies, lixisenatide exposure and variability in exposure are markedly increased regardless of the dose level.

Paediatric population
No studies have been performed with Suliqua in children and adolescents below 18 years of age.

5.3 Preclinical safety data

No animal studies have been conducted with the combination of insulin glargine and lixisenatide to evaluate repeated dose toxicity, carcinogenesis, genotoxicity, or toxicity to reproduction.

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

Lixisenatide
In 2-year subcutaneous carcinogenicity studies, non-lethal C-cell thyroid tumors were seen in rats and mice and are considered to be caused by a non-genotoxic GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. C-cell hyperplasia and adenoma were seen at all doses in rats and a no observed adverse effect level (NOAEL) could be not defined. In mice, these effects occurred at exposure ratio above 9.3-fold when compared to human exposure at the therapeutic dose. No C-cell carcinoma was observed in mice and C-cell carcinoma occurred in rats with an exposure ratio relative to exposure at human therapeutic dose of about 900-fold.
In 2-year subcutaneous carcinogenicity study in mice, 3 cases of adenocarcinoma in the endometrium were seen in the mid dose group with a statistically significant increase, corresponding to an exposure ratio of 97-fold. No treatment-related effect was demonstrated.

Animal studies did not indicate direct harmful effects with respect to male and female fertility in rats. Reversible testicular and epididymal lesions were seen in dogs treated with lixisenatide. No related effect on spermatogenesis was seen in healthy men.
In embryo-foetal development studies, malformations, growth retardation, ossification retardation and skeletal effects were observed in rats at all doses (5-fold exposure ratio compared to human exposure) and in rabbits at high doses (32-fold exposure ratio compared to human exposure) of lixisenatide. In both species, there was a slight maternal toxicity consisting of low food consumption and reduced body weight. Neonatal growth was reduced in male rats exposed to high doses of lixisenatide during late gestation and lactation, with a slightly increased pup mortality observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
85%
Methionine
Metacresol
Zinc
chloride
Concentrated 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

The expiry date of the product is indicated on the packaging materials.

Shelf-life after first use of the pen*:* 14 days

After first use:

Store below 30°C. Do not refrigerate. Do not freeze.
Do not store with attached needle.
Store pen away from direct heat or direct light.
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.

For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Type I colourless glass cartridge with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with inserted laminated sealing disks (bromobutyl rubber on the medicinal product side and polyisoprene on the outside) containing 3 ml of solution. Each cartridge is assembled into a disposable pen.

Packs of 3 and 5 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, the pen must be taken out of the refrigerator and stored below 30°C for 1 to 2 hours.

The cartridge should be inspected 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.

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

A new needle must always be attached before each use. Needles must not be re-used. The patient should discard the needle after each injection. Needles are not included in the pack.

In the event of blocked needles patients must follow the instructions described in the “Instructions for Use” accompanying the package leaflet.

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.

The label must always be checked before each injection to avoid medication errors between Suliqua and other injectable anti-diabetic medicinal products, including the 2 different pens of Suliqua (see section 4.4).
Before using Suliqua, the instructions for use included in the package leaflet must be read carefully.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi-Aventis Israel ltd., P.O.B. 8090, Netanya 4250499.

Revised in January 2022 according to MoH guidelines.