1. NAME OF THE MEDICINAL PRODUCT

Soliqua 100 units/ml + 50 micrograms/ml solution for injection in a pre-filled pen
Soliqua 100 units/ml + 33 micrograms/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Soliqua 100 units/ml + 50 microgram/ml solution for injection in a 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 lixisenatide.
Each dose step contains 1 unit of insulin glargine and 0.5 micrograms of lixisenatide

Soliqua 100units/ml + 33 microgram/ml solution for injection in a pre-filled pen
Each pre-filled pen contains 300 units of insulin glargine and 100 micrograms Lixisenatide in 3 ml solution.
Each ml contains 100 units of insulin glargine and 33 micrograms 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 (injection). SoloStar
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Soliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors. (For study results with respect to effect on glycaemic control, and the populations studied, see section 4.4 and 5.1).

4.2 Posology and method of administration

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

- Soliqua 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** lixisenatide (Soliqua (10-40) pen).
- Soliqua 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** lixisenatide (Soliqua (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 glucagon-like peptide-1 (GLP-1) receptor agonist or oral glucose lowering medicinal product other than metformin and SGLT-2 inhibitors should be discontinued prior to initiation of Soliqua.

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

		Previous		
		Insulin naïve patients (Oral anti-diabetic treatment or GLP-1 receptor agonist)	**Insulin glargine (100 units/ml)** ≥20 to <30 units**	**Insulin glargine (100 units/ml)** ≥30 to ≤60 units**
Starting dose and pen	**Soliqua Solostar (10-40) pen**	10 dose steps (10 units/5 mcg)*	20 dose steps (20 units/10 mcg)*	
	Soliqua Solostar (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 Soliqua 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.

Soliqua 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.

Dosage titration
Soliqua 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 Soliqua (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 Soliqua (30-60) pen.
- If the patient starts with the Soliqua (30-60) pen, the dose may be titrated up to 60 dose steps with this pen.
- For total daily doses >60 dose steps/day, Soliqua 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)
Soliqua 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 Soliqua in patients ≥75 years of age is limited.

Renal impairment
Soliqua 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 Soliqua, 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 Soliqua in patients with hepatic impairment.

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

Method of administration
Soliqua 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).

Soliqua 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 and the batch number of the administered product should be clearly recorded.

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

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia was the most frequently reported observed adverse reaction during treatment with Soliqua

(see section 4.8). Hypoglycaemia may occur if the dose of Soliqua 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 Soliqua should not be given in combination with a sulfonylurea.

The dose of Soliqua 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 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, Soliqua 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. Soliqua has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis and therefore, the use of Soliqua 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. Soliqua 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 Soliqua 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 Soliqua may cause formation of antibodies against insulin glargine and/or lixisenatide. In rare cases, the presence of such antibodies may necessitate adjustment of the Soliqua 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 Soliqua 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.

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

Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is 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 Soliqua have been performed. The information given below is based on studies with the mono components.

Pharmacodynamic interactions
A number of substances affect glucose metabolism and may require dose adjustment of Soliqua.

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 t1/2 were unchanged whatever the timing of its administration (before or after the lixisenatide injection). When administered 1 or 4 hours after 10 mcg lixisenatide, Cmax of paracetamol was decreased by 29% and 31%, respectively and median tmax was delayed by 2.0 and 1.75 hours, respectively. A further delay in tmax and a reduced Cmax of paracetamol have been predicted with the 20 mcg maintenance dose.
No effects on paracetamol Cmax and tmax were observed when paracetamol was administered 1 hour before lixisenatide.

Based on these results, no dose adjustment for paracetamol is required but the delayed tmax 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 t1/2 of ethinylestradiol and levonorgestrel, whereas Cmax of ethinylestradiol was decreased by 52% and 39%, respectively and Cmax of levonorgestrel was decreased by 46% and 20%, respectively and median tmax was delayed by 1 to 3 hours.
The reduction in Cmax 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 Cmax was decreased by 31% and tmax was delayed by 3.25 hours.

No such increase for tmax was observed when atorvastatin was administered in the evening and lixisenatide in the morning but the AUC and Cmax 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 Cmax 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 Cmax was decreased by 63%. The AUC and Cmax of the active metabolite (ramiprilat) were not affected. The tmax 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
Soliqua 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 Soliqua, insulin glargine, or lixisenatide.

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) with insulin glargine indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor foeto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity with insulin glargine.
There are no adequate data from the use of lixisenatide in pregnant women. Studies with lixisenatide in animals have shown reproductive toxicity (see section 5.3).
Soliqua should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Soliqua should be discontinued.

Breast-feeding
It is unknown whether insulin glargine or lixisenatide is excreted in human milk. Soliqua should not be used during breast-feeding.

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

Soliqua 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 Soliqua 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).

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 Soliqua and the comparator.

Documented symptomatic or severe hypoglycaemic adverse reactions

	Insulin naïve patients			**Switch from basal insulin**		**Switch from GLP-1 receptor agonist**	
	Soliqua	**Insulin glargine**	**Lixisenatide**	**Soliqua**	**Insulin glargine**	**Soliqua**	**GLP-1 receptor agonist**
N	469	467	233	365	365	255	256
Documented symptomatic hypoglycaemia*							
Patients with event, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)	146 (40.0)	155 (42.5)	71 (27.8%)	6 (2.3%)
Events per patient-year, n	1.44	1.22	0.34	3.03	4.22	1.54	0.08
Severe hypoglycaemia**							
Events per patient-year, n	0	<0.01	0	0.02	<0.01	<0.01	0

* 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 Soliqua, 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 Soliqua 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 Soliqua may cause formation of antibodies against insulin glargine and/or lixisenatide.

The incidence of formation of anti-insulin glargine antibodies was 21.0% 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 taking insulin containing therapy, including Soliqua have experienced erythema, local oedema, and pruritus at the site of injection.

Heart rate
Increase in heart rate has been reported with GLP-1 receptor 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 Soliqua.

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

4.9 Overdose

Hypoglycaemia and gastrointestinal adverse reactions may develop if a patient is dosed with more Soliqua 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
Soliqua 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
Soliqua
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 Soliqua, 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 Soliqua on glycaemic control were evaluated in three randomised clinical studies in patients with type 2 diabetes mellitus:
- Add-on to metformin [Insulin Naïve]
- Switch from basal insulin
- Switch from GLP-1 receptor agonist

In each of the active-controlled trials, treatment with Soliqua produced clinically and statistically significant improvements in haemoglobin 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 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 Soliqua 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 a sodium-glucose co-transporter-2 (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 7.0% 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 Soliqua, insulin glargine or lixisenatide. Of the 1479 patients who started the run-in phase, 1170 were randomised. The main reasons for not entering the randomized 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/m2 with 63.4% of patients having a BMI ≥30 kg/m2. 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, Soliqua 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.

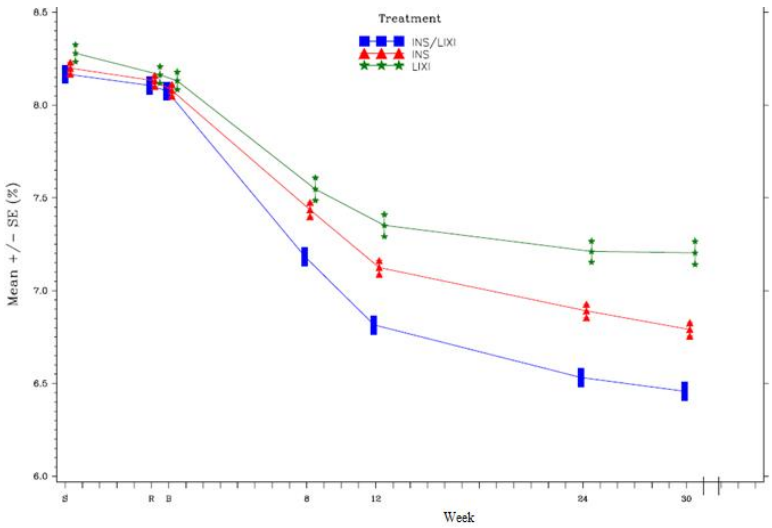
Results at 30 weeks - Add-on to metformin clinical study (mITT population)

	Soliqua	**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) [95% confidence interval]		-2.38 (-2.79 to -1.96)	
LS difference versus lixisenatide (mean) [95%CI]			-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 <7.0% 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: Mean HbA1c (%) by visit during 30-week randomised treatment period - mITT population



Patients in the Soliqua 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 Soliqua 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 Soliqua 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, multicentre study to evaluate the efficacy and safety of Soliqua

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 Soliqua (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 95.0% received at least 1 concomitant OAD.

At Week 30, Soliqua 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.

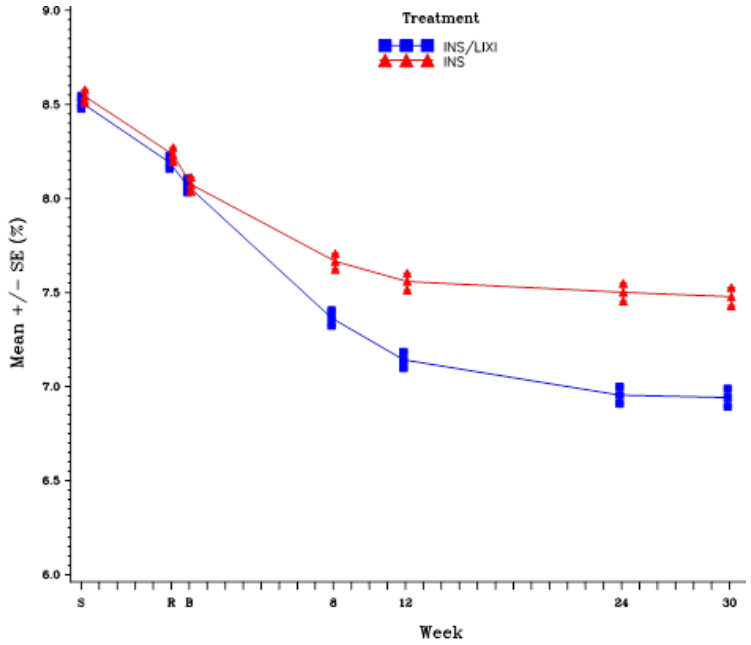
Results at 30 weeks -Study Type 2 Diabetes Uncontrolled on Basal Insulin mITT population

	Soliqua	**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%CI]	-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 to26.7] (<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: Mean HbA1c (%) by visit during 30-week randomised treatment period - mITT population



Switch from GLP-1 receptor agonist
Clinical study in patients with Type 2 diabetes insufficiently controlled on GLP-1 receptor agonist
The efficacy and safety of Soliqua compared to unchanged pre-trial GLP-1 receptor agonist treatment were studied in a 26-week, randomized, open-label trial. The trial included 514 patients with type 2 diabetes mellitus inadequately controlled (HbA1c level of 7% to 9% both inclusive) while treated for at least 4 months with liraglutide or exenatide or for at least 6 months with dulaglutide, albiglutide or exenatide extended release, all at maximal tolerated dose, and metformin alone or in combination with pioglitazone, a SGLT-2 inhibitor or both. Eligible patients were randomized to either receive Soliqua or to continue their previous GLP-1 receptor agonist both on top of their previous oral anti-diabetic treatment.

At screening 59.7% of the subjects received a once or twice-daily GLP-1 receptor agonist and 40.3% received a once weekly GLP-1 receptor agonist. At screening, 6.6% of the subjects received pioglitazone, and 10.1% a SGLT-2 inhibitor in combination with metformin. The study population had the following characteristics: mean age was 59.6 years, 52.5% of the subjects were male. The mean duration of diabetes was 11 years, the mean duration of previous GLP-1 receptor agonist treatment was 1.9 years, the mean BMI was approximately 32.9 kg/m^2, mean eGFR was 87.3 ml/min/1.73 m^2 and 90.7% of patients had an eGFR ≥60 ml/min.

At week 26, Soliqua provided statistically significant improvement in HbA1c (p <0.0001). A pre-specified analysis by GLP-1 receptor agonist subtype (once/twice daily or weekly formulation) used at screening showed that HbA1c change at week 26 was similar for each subgroup and consistent with the primary

analysis for the overall population. The mean daily dose of Soliqua at Week 26 was 43.5 dose steps.

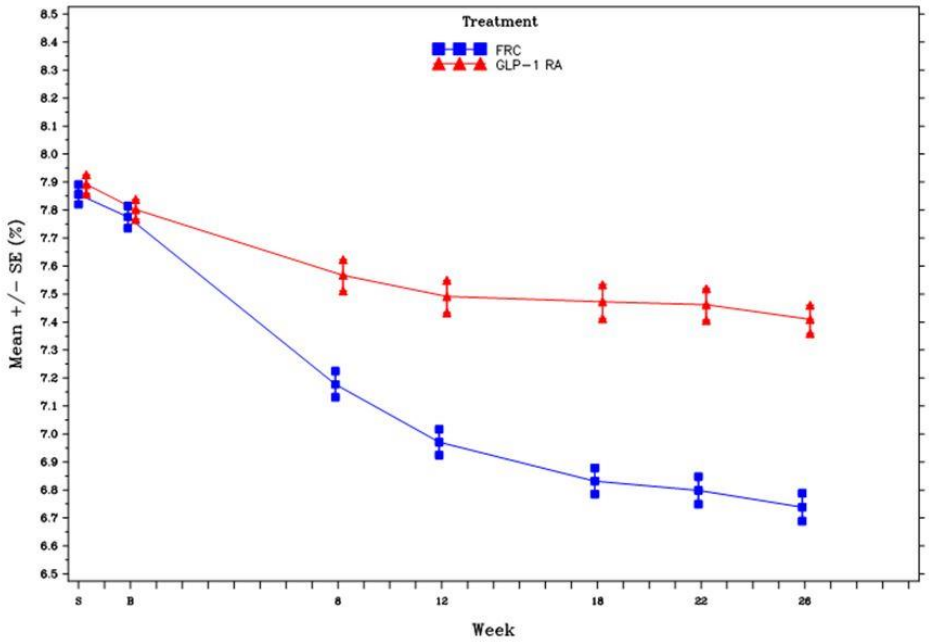
See table and figure below for the other endpoints in the study.

Results at 26 weeks -Study Type 2 Diabetes Uncontrolled on GLP-1 receptor agonist mITT population

	Soliqua	**GLP-1 receptor agonist**
Number of subjects (mITT)	252	253
HbA1c (%)		
Baseline (mean; post run-in phase)	7.8	7.8
End of treatment (mean)	6.7	7.4
LS change from baseline (mean)	-1.0	-0.4
Difference versus GLP-1 receptor agonist [95% confidence interval] (p-value)	-0.6 [-0.8, -0.5] (<0.0001)	
Patients [n (%)] reaching HbA1c <7% at week 26	156 (61.9%)	65 (25.7%)
Proportion difference (95% confidence interval) vs GLP-1 receptor agonist	36.1% (28.1% to 44.0%)	
p-value	<.0001	
Fasting plasma glucose (mmol/L)		
Baseline (mean)	9.06	9.45
End of study (mean)	6.86	8.66
LS change from baseline (mean)	-2.28	-0.60
Difference versus GLP-1 receptor agonist [95% confidence interval] (p-value)	-1.67 (-2.00 to -1.34) (<0.0001)	
2 hour PPG (mmol/L)*		
Baseline (mean)	13.60	13.78
End of study (mean)	9.68	12.59
LS change from baseline (mean)	-4.0	-1.11
LS difference versus GLP-1 receptor agonist (mean) [95% confidence interval] (p-value)	-2.9 (-3.42 to -2.28) (<0.0001)	
Mean body weight (kg)		
Baseline (mean)	93.01	95.49
LS change from baseline (mean)	1.89	-1.14
Comparison versus GLP-1 receptor agonist [95% confidence interval] (p-value)	-3.03 (2.417 to 3.643) (<0.0001)	

*2 hour PPG minus the pre-meal glucose value

Figure: Mean HbA1c (%) by visit during 26-week randomized treatment period- mITT population



Concomitant use of Soliqua with SGLT-2 inhibitors (SGLT2i)
The concomitant use of Soliqua with SGLT2i is supported by subgroup analyses from three Phase 3 randomized clinical trials (119 patients on the insulin glargine/lixisenatide fixed ratio combination (FRC) who also received SGLT2i).

One study conducted in Europe and North America included data from 26 patients (10.1%) who concomitantly received insulin glargine/lixisenatide FRC, metformin and an SGLT2i. Two more Phase 3 studies from the dedicated Japanese clinical development program performed in patients not reaching sufficient glycaemic control on OADs provided data for 59 patients (22.7%) and 34 patients (21.1%), respectively, who concomitantly received SGLT2i and insulin glargine/lixisenatide FRC.

The data from these 3 studies show that initiation of Soliqua in patients inadequately controlled with a treatment including SGLT2i leads to improved change in HbA1c versus the comparators. There was no increased risk of hypoglycemia and no relevant differences in the overall safety profile in SGLT2i users compared to non-users.

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

Insulin glargine
The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomised, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of 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 LANTUS 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 cardiovascular (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: Cardiovascular 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Soliqua in all subsets of the paediatric population for treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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 tmax of lixisenatide was in the range of 2.5 to 3.0 hours. AUC was comparable while there was a small decrease in Cmax 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
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. The apparent volume of distribution of insulin glargine after subcutaneous administration of the insulin glargine/lixisenatide combinations (Vss/F) is approximately 1700 L.

Biotransformation and elimination
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. After multiple-dose administration 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 trials in 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 Soliqua 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 tumours 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

24 months.
Shelf-life after first use of the pen*:* 28 days

For in-use pens
Store below 25°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 in use storage conditions, 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.

Needles are not included in the pack.
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 25°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.

Soliqua 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.

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 Soliqua and other injectable anti-diabetic medicinal products, including the 2 different pens of Soliqua (see section 4.4). Before using Soliqua, 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.

MANUFACTURER
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

DATE OF REVISION
Sept 2020 (EU SmPC Mar 2020_PRAC)

Instructions For Use Video: https://surl.sanofi.com/soliquasgifu

Soliqua 100 units/ml + 50 micrograms/ml solution for injection in a pre-filled pen (10-40). INSTRUCTIONS FOR USE

Read the Package Leaflet and these Instructions for Use first

Soliqua (10-40) pen contains insulin glargine and lixisenatide. The combination of medicinal products in this pen is for the daily injection of 10 to 40 dose steps of Soliqua.

- **Never re-use needles.** If you do, you might not get your full dose (underdosing) or get too much (overdosing) as the needle could block.
- **Never use a syringe to remove medicine from your pen.** If you do, you may not get the correct amount of medicine.

Keep these Instructions For Use for future reference.

Important information

- Never share your pen – it is only for you
- Never use your pen if it is damaged or if you are not sure that it is working properly.
- Always perform a safety test. (See **STEP 3**).
- Always carry a spare pen and spare needles in case they get lost or stop working.
- Always check the label of the pen before use to make sure you have the correct pen.

Learn to inject:

- Talk with your healthcare provider about how to inject, before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get too much or too little medicine.

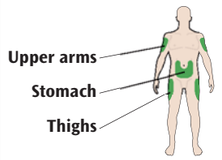
Need help?

If you have any questions about Soliqua, the pen or about diabetes, ask your doctor, pharmacist or nurse or call the local sanofi-aventis number.

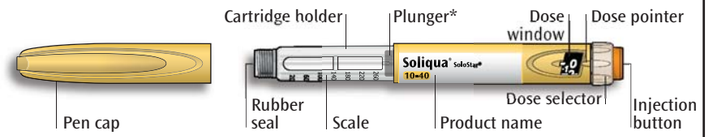
Extra items you will need:

- a new sterile needle (see **STEP 2**).
- a sharps container for used needles and pens. (see **Throwing your pen away**).

Places to inject



Get to know your pen



*You will not see the plunger until you have injected a few doses

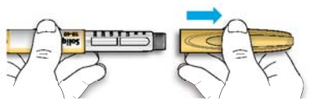
STEP 1: Check your pen

Take a new pen out of the refrigerator at least **1** hour before you inject. Injecting cold medicine is more painful.

A. Check the name and expiry date on the label of your pen.

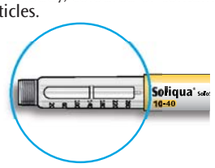
- Make sure you have the correct medicine. This pen is peach coloured with an orange injection button.
- **Do not use this pen if you need a daily dose less than 10 dose steps or if you need more than 40 dose steps. Discuss with your doctor which pen is suitable for your needs.**
- **Do not** use your pen after the expiry date.

B. Pull off the pen cap.



C. Check that the medicine is clear.

- **Do not** use the pen if the medicine looks cloudy, coloured or contains particles.

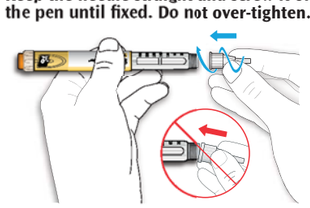


STEP 2: Attach a new needle

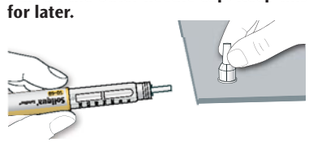
- **Do not** reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination, and infection.
- Always use needles that are compatible for use with Soliqua pen.

A. Take a new needle and peel off the protective seal.

B. Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



C. Pull off the outer needle cap. Keep this for later.



D. Pull off the inner needle cap and throw away.

Handling needles

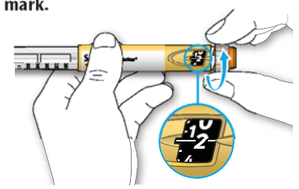
- Take care when handling needles to prevent needle injury and cross-infection.

STEP 3: Do a safety test

Always do a safety test before each injection to:

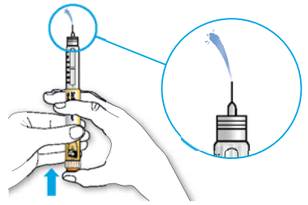
- Check your pen and the needle to make sure they are working properly
- Make sure that you get the correct dose.

A. Select 2 dose steps by turning the dose selector until the dose pointer is at the 2 mark.



B. Press the injection button all the way in.

- When medicine comes out of the needle tip, your pen is working correctly, the dose selector will be reset to "0".



If no liquid appears:

- You may need to repeat this step up to 3 times before seeing medicine.
- If no medicine comes out after the third time, the needle may be blocked. If this happens:
  - change the needle (**see STEP 6 and STEP 2**),
  - then repeat the safety test (**STEP 3**).
- **Do not** use your pen if there is still no medicine coming out of the needle tip. Use a new pen.
- **Do not** use a syringe to remove medicine from your pen.

If you see air bubbles

- You may see air bubbles in the medicine. This is normal, they will not harm you.

STEP 4: Select the dose

- **Use this pen only to inject single daily doses from 10 to 40 dose steps.**
- **Do not** select a dose or press the injection button without a needle attached. This may damage your pen.

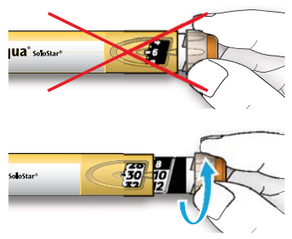
A. Make sure a needle is attached and the dose is set to '0'.

B. Turn the dose selector until the dose pointer lines up with your dose.

- If you turn past your dose, you can turn back down.
- If there are not enough dose steps left in your pen for your dose, the dose selector will stop at the number of dose steps left.
- If you cannot select your full prescribed dose, use a new pen or inject the remaining dose steps and use a new pen to complete your dose. Only in this case, it is okay to inject a partial dose of less than 10 dose steps. Always use another Soliqua (10-40) pen to complete your dose and no other pen.

How to read the dose window

- **Do not** use the pen if your single daily dose is less than 10 dose steps, shown as white numbers on a black background.



Units of medicine in your pen

- Your pen contains a total of 300 dose steps. You can select your dose in steps of 1 dose step.
- **Do not** use this pen if you need a single daily dose that is less than 10 dose steps, or more than 40 dose steps.
- Each pen contains more than 1 dose.

STEP 5: Inject the dose

- If you find it hard to press the injection button in, **do not** force it as this may break your pen:
- Change the needle (**see STEP 6** "Remove the needle" **and STEP 2** "Attach a new needle") then do a safety test (**see STEP 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove medicine from your pen.

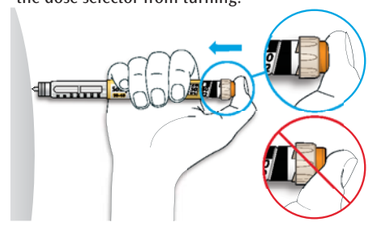
A. Choose a place to inject as shown in the picture above.

B. Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.

C. Place your thumb on the injection button. Then press all the way in and hold.

- **Do not** press at an angle. Your thumb could block the dose selector from turning.



D. Keep the injection button held in and when you see "0" in the dose window, slowly count to 10.

- This will make sure you get your full dose.

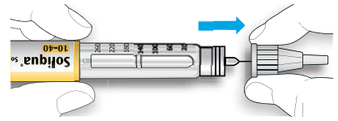
E. After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin.

STEP 6: Remove the needle

- Take care when handling needles to prevent needle injury and cross-infection.
- **Do not** put the inner needle cap back on.

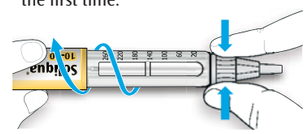
A. Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.

- The needle can puncture the cap if it is recapped at an angle.



B. Grip and squeeze the widest part of the outer needle cap.
Turn your pen several times with your other hand to remove the needle.

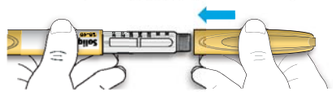
- Try again if the needle does not come off the first time.



C. Throw away the used needle in a puncture resistant container (see **"Throwing your pen away"** at the end of this Instructions for Use).

D. Put your pen cap back on.

- Do not put the pen back in the refrigerator.



How to store your pen

Before first use

- Keep new pens in the refrigerator between **2°C to 8°C**.
- **Do not** freeze.

After first use

- Keep your pen at room temperature, **below 25°C**.
- **Do not** put your pen back in the refrigerator.
- **Do not** store your pen with the needle attached.
- Store the pen with your pen cap on.
- Only use your pen for up to **28 days** after its first use.

How to care for your pen

Handle your pen with care

- If you think that your pen may be damaged, **do not** try to fix it. Use a new one.

Protect your pen from dust and dirt

- You can clean the outside of your pen by wiping it with a damp cloth (water only). **Do not** soak, wash or lubricate the pen. This may damage it.

Throwing your pen away

- Remove the needle before throwing your pen away.
- Throw away your used pen as instructed by your pharmacist or local authority.

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