

Soliqua[®]

Solution for injection in a pre-filled pen
Insulin glargine and Lixisenatide

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 in pre-filled pen (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 pre-filled 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 therapy		
		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 (10-40) pen	10 dose steps (10 units/5 mcg)*	20 dose steps (20 units/10 mcg)*	
	Soliqua (30-60) pen			30 dose steps (30 units/10 mcg)*

* units insulin glargine (100 units/mL) / mcg lixisenatide

Patients on less than 20 units of insulin glargine may be considered similar to insulin naïve patients.

**** 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.

Dose 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).

Missed dose

If a dose of Soliqua is missed, it should be injected within the hour prior to the next meal.

Special population

Elderly

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.

Type 1 diabetes mellitus

Soliqua 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 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.

Antidiabetic medicinal products not studied in combination with Soliqua

Soliqua 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 Soliqua 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 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 $t_{1/2}$ 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

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 malformative nor fetoneonatal 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).

Soliqua 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 Soliqua.

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: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ 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	Rare	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	Delayed gastric emptying	
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.

*** Liraglutide, exenatide BID (twice in a day) or extended release, dulaglutide or albiglutide

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 using 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.

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 GLP1 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 clinical studies, 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 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 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)

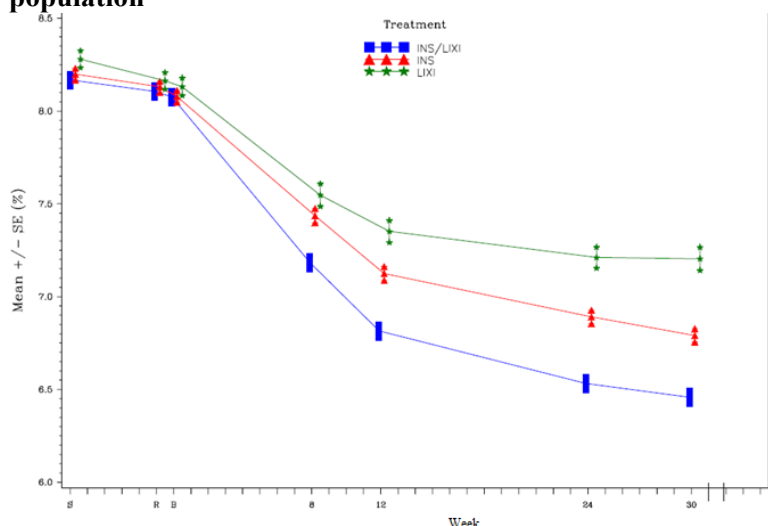
	Soliqua	Insulin glargine	Lixisenatide
Number of subjects (mITT)	468	466	233
HbA1c (%)			
Baseline (mean; post run-in phase)	8.1	8.1	8.1
End of study (mean)	6.5	6.8	7.3
LS change from baseline (mean)	-1.6	-1.3	-0.9
Difference vs. insulin glargine [95% confidence interval] (p-value)		-0.3 [-0.4, -0.2] (<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% 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 <7.0% 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, multicenter 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 \leq 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/m² with 57.3% of patients having a BMI \geq 30 kg/m². 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

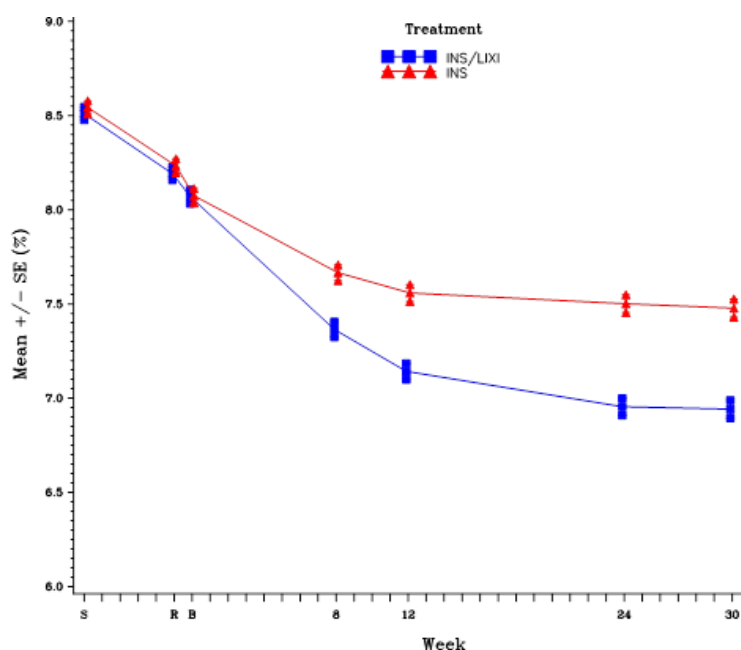
	Soliqua	Insulin glargine
Number of subjects (mITT)	366	365
HbA1c (%)		
Baseline (mean; post run-in phase)	8.1	8.1
End of treatment (mean)	6.9	7.5
LS change from baseline (mean)	-1.1	-0.6
Difference versus insulin glargine [95% confidence interval] (p-value)		-0.5 [-0.6, -0.4] (<0.0001)
Patients [n (%)] 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% 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: 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/m², mean eGFR was 87.3 ml/min/1.73 m² and 90.7% of patients had an eGFR \geq 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.

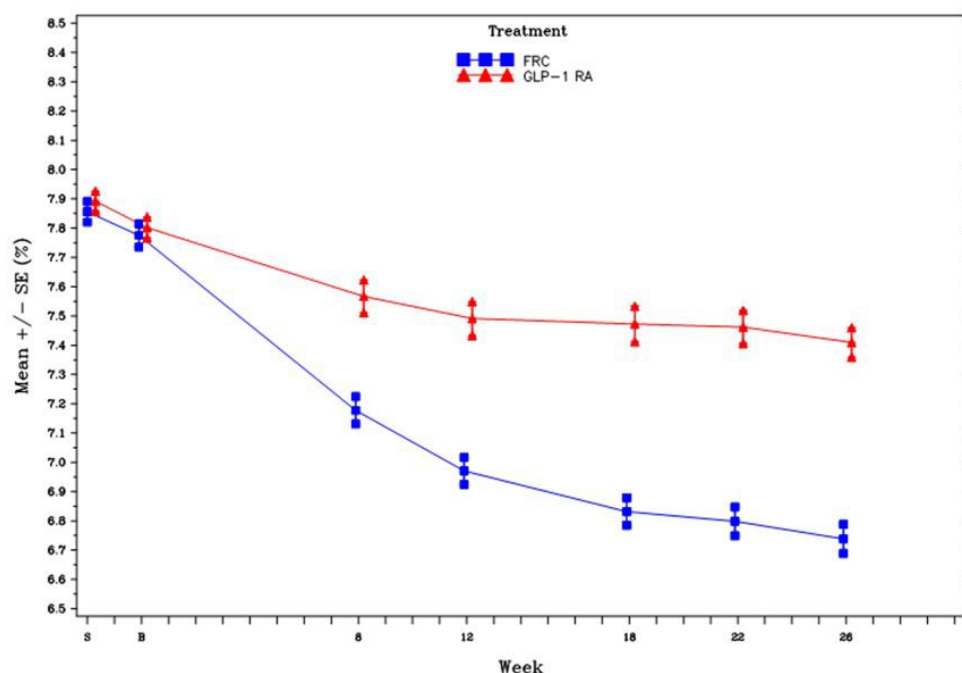
Results at 26 weeks -Study Type 2 Diabetes Uncontrolled on GLP-1 receptor agonist mITT population

	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)

* Liraglutide, exenatide BID or extended release, dulaglutide or albiglutide

**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 (insulin glargine, lixisenatide, liraglutide, exenatide BID or extended release, dulaglutide or albiglutide). 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 insulin glargine 100 Units to 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 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 in the 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 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 (V_{ss}/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 (V_z/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 studies 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

Please refer to the outer box.

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.

Ref : EMA SmPC Dec2022

Package leaflet: information for the user

Soliqua 100 units/ml + 33 micrograms/mL solution for injection in a pre-filled pen Insulin glargine + lixisenatide

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

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

What is in this leaflet:

1. What Soliqua is and what it is used for
2. What you need to know before you use Soliqua
3. How to use Soliqua
4. Possible side effects
5. How to store Soliqua
6. Contents of the pack and other information

1. What Soliqua is and what it is used for

Soliqua is an injectable diabetes medicine that contains two active substances:

- insulin glargine: a long acting type of insulin which helps control blood sugar (glucose) throughout the day.
- Lixisenatide: a “GLP-1 analogue” that helps the body produce its own additional insulin in response to increases in blood sugar, and slows the absorption of sugar from foods.

Soliqua is used to treat adults with type 2 diabetes, to help control blood sugar levels when they are too high, it is an adjunct to diet and exercise. It is given with metformin with or without sodium-glucose co-transporter-2 (SGLT-2) inhibitors (gliflozin products), when other medicines are not enough on their own to control your blood sugar levels.

2. What you need to know before you use Soliqua

Do not use Soliqua:

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Soliqua if:

- you have type 1 diabetes, as Soliqua is used for type 2 diabetes and this medicine will not be right for you.
- you have diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to use glucose because there is not enough insulin) since this medicine will not be right for you.
- you have a severe stomach or gut problem such as a disease of the muscles of the stomach called “gastroparesis” which results in delayed stomach emptying. Since Soliqua may cause stomach side effects, the medicine has not been studied in patients with severe stomach or gut problems.

Please see the information regarding medicines that should not stay too long in your stomach in the section “**Other medicines and Soliqua**”.

- you have severe kidney disease or you are on dialysis as the use of this medicine will not be recommended

Follow closely your doctor’s instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) and injection technique.

Be especially aware of the following:

- Too low blood sugar (hypoglycaemia). If your blood sugar is too low, follow the guidance for hypoglycaemia (see information in the box at the end of this leaflet).
- Too high blood sugar (hyperglycaemia). If your blood sugar is too high, follow the guidance for hyperglycaemia (see information in the box at the end of this leaflet).
- Ensure that you use the right medicine. You must always check the label before each injection to avoid mix-ups between Soliqua and other insulins.
- If you have poor eyesight, please see section 3.

While using this medicine be aware of the following and talk to doctor, pharmacist or nurse before using Soliqua :

- severe pain in your stomach area (abdomen) that will not go away. This could be a sign of inflamed pancreas (acute pancreatitis).
- loss of fluids from your body (dehydration) e.g. in case of vomiting and diarrhoea. It is important to avoid dehydration by drinking plenty of fluids, especially during the first weeks of treatment with Soliqua.

Skin changes at the injection site

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Soliqua). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medicine dose.

Travel

Talk to your doctor before travelling. You may need to talk about:

- If your medicine is available in the country you are visiting.
- How to arrange the supply of your medicine, needles and other items.
- How to correctly store your medicine while travelling.
- The time you eat meals and use your medicine.
- The possible effects of changing to different time zones.
- Any health risks in the countries you will visit.
- What you should do in an emergency if you feel unwell or become ill.

Children and adolescents

There is no experience with Soliqua in children and adolescents aged less than 18 years, therefore, the use of Soliqua is not recommended in this age group.

Other medicines and Soliqua

Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines. If you use another antidiabetic medicine, discuss with your doctor whether you should stop using that medicine when starting Soliqua.

Some medicines can change your blood sugar level. This may mean your doctor may need to change your Soliqua dose. So, before taking a medicine ask your doctor if it will affect your blood sugar and what action, if any, you need to take. You also need to be careful when you stop taking a medicine.

The effect of some medicines you swallow might be affected by Soliqua. Some medicines such as antibiotics, oral contraceptives, statins (medicines like atorvastatin to lower cholesterol) gastro resistant tablets or capsules or granules or oral powder or suspensions that should not stay too long in your stomach may need to be taken at least one hour before or four hours after your Soliqua injection.

Your blood sugar level may fall (hypoglycaemia) if you take:

- Any other medicine to treat diabetes.
- Disopyramide, for some heart problems.
- Fluoxetine, for depression.
- Sulfonamide antibiotics, to treat infections.
- Fibrates, for lowering high levels of blood fats.
- Monoamine oxidase inhibitors (MAOIs), for depression or Parkinson's disease.
- Angiotensin converting enzyme (ACE) inhibitors, for heart problems or high blood pressure.
- Medicines to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates (such as acetylsalicylic acid).
- Pentamidine, for some parasite infections. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Your blood sugar level may rise (hyperglycaemia) if you take:

- Corticosteroids such as cortisone and prednisolone, for inflammation.
- Danazol, for endometriosis.
- Diazoxide, for high blood pressure.
- Protease inhibitors, for HIV.
- Diuretics, for high blood pressure or fluid retention.
- Glucagon, for very low blood sugar.
- Isoniazid, for tuberculosis.
- Somatropin, a growth hormone.
- Thyroid hormones, for thyroid gland problems.
- Oestrogens and progestogens, such as in the contraceptive pill for birth control or use of oestrogens for bone loss (osteoporosis).
- Clozapine, olanzapine and phenothiazine derivatives, for mental health problems.
- Sympathomimetic medicines such as epinephrine (adrenaline), salbutamol and terbutaline, for asthma.

Your blood sugar level may either rise or fall if you take:

- Beta-blockers or clonidine, for high blood pressure.
- Lithium salts, for mental health problems.

Medicine that may reduce warning signs of low blood sugar

Beta-blockers and some other medicines (such as clonidine, guanethidine, reserpine, for high blood pressure) may make it harder to recognise warning signs of your low blood sugar levels (hypoglycaemia). It can even hide or stop the first signs that your blood sugar is too low.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using this medicine.

Warfarin or other anticoagulants

Tell your doctor if you are taking warfarin or other anticoagulants (medicines used to prevent clotting of the blood) as you might need to have more frequent blood tests (called 'International Normalised Ratio' or INR test) to check your blood clotting.

Soliqua with alcohol

Your blood sugar level may either rise or fall if you drink alcohol. You should check your blood sugar level more often.

Pregnancy and breast-feeding

Soliqua should not be used during pregnancy. It is not known if Soliqua harms your unborn child.

Soliqua should not be used if breast-feeding. It is not known if Soliqua passes into your milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Having too low or too high blood sugar (see information in the box at the end of this leaflet) can affect your ability to drive and use tools or machines. Your concentration may be affected. This could be dangerous to yourself and others.

Ask your doctor whether you can drive if:

- Your blood sugar is often too low.
- You find it hard to recognise when your blood sugar is too low.

Soliqua contains sodium

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

Soliqua contains metacresol

This medicine contains metacresol which may cause allergic reactions.

3. How to use Soliqua

Always use this medicine exactly as your doctor has told you. Your doctor may tell you to use a different dose of Soliqua compared to your previous insulin dose or glucose lowering medicine if any. Check with your doctor, pharmacist or nurse if you are not sure.

Based on your lifestyle, your blood sugar tests and your previous insulin use, your doctor will tell you:

- How much Soliqua you need each day and at what time.
- When to check your blood sugar level and if you need to carry out urine tests.
- When you may need a higher or lower dose.

Your doctor may tell you to use Soliqua with other medicines for high blood sugar.

How much to use

The Soliqua 100 units/mL + 33 micrograms/mL solution for injection in pre-filled pen:

- This pen provides a dose of 30 to 60 dose steps in one injection, in steps of 1 dose step.
- Each dose step of Soliqua you dial contains 1 unit of insulin glargine and 0.33 micrograms of lixisenatide.

Your dose of Soliqua is administered as 'dose steps'. The dose window on the pen shows the number of dose steps.

Do not inject a dose lower than 30 dose steps. Do not inject a dose higher than 60 dose steps.

If a dose lower than 30 dose steps is needed, your doctor will prescribe a different strength. For dose steps from 10-40 units, Soliqua 100 units/ml + 50 micrograms/ml solution for injection in pre-filled pen

Many factors may affect your blood sugar level. You should know what they are so that you can take the right action if your blood sugar level changes and help stop it becoming too high or too low. See the box at the end of this leaflet for more information.

Use in elderly patients (65 years and over)

If you are 65 years or older, talk to your doctor as you may need a lower dose.

If you have kidney or liver problems

If you have kidney or liver problems, talk to your doctor as you may need a lower dose.

When to inject Soliqua

Use Soliqua once a day, within 1 hour before a meal. Preferably inject Soliqua before the same meal every day, when you have chosen the most convenient meal.

Before injecting Soliqua

- Always follow the “Instructions for use” that come with this package leaflet and use the pen as described.
- If you do not follow all of these instructions, you may get too much or too little of Soliqua.

To avoid mistakes, always check the medicine pack and label on the pen before each injection to make sure you have the correct pen, especially if you inject more than one medicine. Ask your doctor or pharmacist if you are not sure.

How to inject

- Soliqua is injected under the skin (subcutaneous use or “SC”).
- Inject it into the front of your thighs, upper arms or the front of your waist (abdomen).
- Change the place within the area you inject each day. This will reduce the risk of developing dents or lumps at the site (for more information, see “Other side effects” in section 4).

Do not use Soliqua:

- If there are particles in the Soliqua. The solution should be clear, colourless and water-like.

Other important information about using the pre-filled pens

- Always use a new needle for each injection. The re-use of needles increases the risk of blocked needles which may cause under- or overdosing. Dispose of the needle safely after each use.
- To prevent infection being passed from one person to another, pens should never be used for more than one person, even when the needle is changed
- Only use needles that are compatible for use with Soliqua pen (see “Instructions for Use”).
- A safety test must be performed before each injection.
- Throw away the used needle in a sharps container, or as told by your pharmacist or local authority.

Never use a syringe to remove the solution from the pen to avoid dosing errors and potential overdose.

If the pen is damaged, has not been stored correctly, if you are not sure that it is working properly or you notice that your blood sugar control is unexpectedly getting worse:

- throw the pen away and use a new one.
- talk to your doctor, pharmacist or nurse if you think you have a problem with your pen.

If you use more Soliqua than you should

If you have injected too much of this medicine, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar and eat more food to prevent your blood sugar getting too low (hypoglycaemia). If your blood sugar gets too low, see the advice in the box at the end of this leaflet.

If you forget to use Soliqua

If you have missed a dose of Soliqua or if you have not injected enough insulin, your blood sugar level may become too high (hyperglycaemia):

When needed, Soliqua can be injected before the next meal.

- Do not inject a double dose to make up for a forgotten dose.
- Do not take two injections per day
- Check your blood sugar and then inject your next dose at the usual time.
- For information on the treatment of hyperglycaemia, see the box at the end of this leaflet.

If you stop using Soliqua

Do not stop using this medicine without talking to your doctor. If you do, it could lead to very high blood sugar (hyperglycaemia) and a build-up of acid in the blood (ketoacidosis).

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

4. Possible side effects

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

If you notice signs of your blood sugar being too low (hypoglycaemia), take action to increase your blood sugar level straight away (see the box at the end of this leaflet).

Hypoglycaemia can be very serious and is very common with medicine containing insulin (may affect more than 1 in 10 people).

Low blood sugar means that there is not enough sugar in your blood.

If your blood sugar falls too low, you may pass out (become unconscious).

If blood sugar remains very low for too long it may cause brain damage and may be life-threatening.

For more information, see the box at the end of this leaflet.

Other side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

• Skin changes at the injection site:

If you inject insulin too often in the same place, the skin may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by a build-up of a protein called amyloid (cutaneous amyloidosis;). This is not known how often these skin changes occur. The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

Common: may affect up to 1 in 10 people

- Feeling dizzy
- Feeling sick (Nausea)
- Vomiting
- Diarrhoea
- Skin and allergic reactions at the injection site: The signs may include reddening, unusually intense pain when injecting, itching, hives, swelling or inflammation. This can spread around the injection site. Most minor reactions to insulins usually disappear in a few days to a few weeks.

Uncommon: may affect up to 1 in 100 people

- Cold, runny nose, sore throat
- Hives (urticaria)
- Headache.
- Indigestion (dyspepsia)

- Stomach ache
- Tiredness

Rare (may affect up to 1 in 1,000 people)

- A delay in the emptying of the stomach

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Soliqua

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

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

Before first use

Store in a refrigerator (2°C-8°C).

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

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

After first use

Store your pen in use below 25°C for a maximum of 28 days. Discard the pen after this period.

Do not return the pen to a refrigerator and do not freeze. Store the pen away from direct heat or direct light. Always keep the cap on the pen when you are not using it in order to protect it from light.

Do not leave the pen in a car on an exceptionally warm or cold day.

Do not store the pen with the needle attached.

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

6. Contents of the pack and other information

What Soliqua contains

- The active substances Soliqua are insulin glargine and lixisenatide.
Each pen contains 300 units insulin glargine and 100 micrograms lixisenatide in 3 ml of solution.
Each mL contains 100 units insulin glargine and 33 micrograms lixisenatide
Each dose step of Soliqua contains 1 unit of insulin glargine and 0.33 micrograms of lixisenatide.
- The other ingredients are: 85% glycerol, methionine, metacresol, zinc chloride, concentrated hydrochloric acid, and sodium hydroxide (for pH adjustment) and water for injections. See also section 2 “What you need to know before you use Soliqua” for information on sodium and metacresol.

What Soliqua looks like and contents of the pack

Soliqua is a clear and colourless solution for injection (injection) filled in a glass cartridge inserted in a pre-filled pen (Solostar).

Packs of 3 and 5 pre-filled pens.

Not all pack sizes may be marketed in your country.

Needles are not included in the pack.

Manufacturer:

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
65926 Frankfurt am Main
Germany

This leaflet was last revised in : Dec2022

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

If you use insulin, you should always carry the following things with you:

- Foods containing sugar, such as dextrose or a sugary drink (at least 20 grams).
- Information so that others know you have diabetes.

Hyperglycaemia (high blood sugar levels)

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

Reasons why hyperglycaemia may happen:

Examples include:

- You have not injected your Soliqua or not injected enough.
- Your medicine has become less effective – for example because it was not stored properly.
- Your pen does not work properly.
- You are doing less exercise than usual.
- You are under stress – such as emotional distress or excitement.
- You have an injury, infection or fever or have had an operation.
- You are taking or have taken certain other medicines (see section 2, "Other medicines and Soliqua").

Warning signs of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heartbeat, and urine test showing glucose and ketone bodies. Stomach pain, fast and deep breathing, feeling sleepy or passing out (becoming unconscious) may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What to do if you experience hyperglycaemia

- Test your blood sugar level and, if it is high and as agreed with your doctor or nurse, test your urine for ketones as soon as you notice any of the above signs
- Contact your doctor straight away if you have severe hyperglycaemia or ketoacidosis. This must always be treated by a doctor, normally in a hospital.

Hypoglycaemia (low blood sugar levels)

If your blood sugar level falls too much you may pass out (become unconscious). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You should learn to recognise the signs when your blood sugar is falling – so you can take action to stop it getting worse.

Reasons why hypoglycaemia may happen:

Examples include:

- You inject too much Soliqua.
- You miss meals or delay them.
- You do not eat enough, or eat food containing less carbohydrates than normal – artificial sweeteners are not carbohydrates.
- You drink alcohol – especially when you have not eaten much.
- You lose carbohydrates from being sick (vomiting) or diarrhoea.
- You are doing more exercise than usual or a different type of physical activity.
- You are recovering from an injury, operation or other stress.
- You are recovering from an illness or from fever.

You are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Soliqua").

Hypoglycaemia is also more likely to happen if:

- You have just started Soliqua treatment – if low blood sugar occurs, it may be more likely to happen in the morning.
- Your blood sugar levels are almost normal or are unstable.
- You change the area where you inject Soliqua. For example from the thigh to the upper arm.
- You have severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning signs of hypoglycaemia

The first signs may be in your body generally. Examples of signs that your blood sugar level is falling too much or too fast include: sweating, clammy skin, feeling anxious, fast or irregular heartbeat, high blood pressure and palpitations. These signs often develop before the signs of a low sugar level in the brain.

Other signs include: headaches, feeling very hungry, feeling sick (nausea) or being sick (vomiting), feeling tired, sleepy, restless, sleeping problems, aggressive behaviour, difficulty concentrating, slow reactions, depression, feeling confused, difficulty speaking (sometimes total loss of speech), changes in your sight, trembling, being unable to move (paralysis), tingling in the hands or arms, feeling numb and tingling often around the mouth, feeling dizzy, loss of self-control, being unable to look after yourself, fits, passing out.

When the signs of hypoglycaemia may be less clear:

The first warning signs of hypoglycaemia may change, be weaker or missing altogether if:

- You are elderly.
- You have had diabetes for a long time.
- You have a certain type of nerve damage (called "diabetic autonomic neuropathy").
- You have recently had too low blood sugar (for example the day before).
- Your low blood sugar comes on slowly.
- Your low blood sugar is always around "normal" or your diabetes control has greatly improved recently.
- You have recently changed from animal insulin to a manufactured insulin, like there is in Soliqua.
- You are taking or have taken certain other medicines (see section 2, "Other medicines and Soliqua").

In such cases, you may develop severe hypoglycaemia (and even pass out) before you know what is happening. Be familiar with your warning signs. If necessary, you might need to test your blood sugar more often. This can help to spot mild hypoglycaemic episodes. If you find it difficult to recognise your warning signs, you should avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do if you experience hypoglycaemia?

1. Do not inject Soliqua. Take about 15 to 20 grams sugar straight away - such as glucose, sugar cubes or a sugary drink. Drink or eat foods that contain artificial sweeteners (such as diet drinks) do **not** help treat low blood sugar.
2. You might then need to eat something (such as bread or pasta) that will raise your blood sugar over a longer time, especially if your next meal is not due. Ask your doctor or nurse if you are not sure which foods you should eat.
With Soliqua, it may take longer to recover from low blood sugar because it contains a long-acting insulin (insulin glargine).
3. Test your blood glucose levels after 10-15 minutes after taking sugar. If blood glucose levels are still too low (<4 mmol/L) or hypoglycaemia comes back take another 15 to 20 grams of sugar.

4. Speak to a doctor straight away if you are not able to control the hypoglycaemia, or it comes back again.

What other people should do if you have hypoglycaemia

Tell your relatives, friends and close colleagues to get medical help straight away if you are not able to swallow or if you pass out (become unconscious).

You will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections should be given even if it is not certain that you have hypoglycaemia.

You should test your blood sugar straight away after taking glucose to check that you really have hypoglycaemia.

Soliqua 100 units/mL + 33 micrograms/mL solution for injection in a pre-filled pen (30-60).

INSTRUCTIONS FOR USE

Read the Package Leaflet and these Instructions for Use before first use of Soliqua

Soliqua (30-60) pen contains insulin glargine and lixisenatide. The combination of medicinal products in this pen is for the daily injection of 30 to 60 dose steps Soliqua.

- **Never re-use needles.** If you do you might not get your full dose (under dosing) 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 doctor or pharmacist or nurse 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.

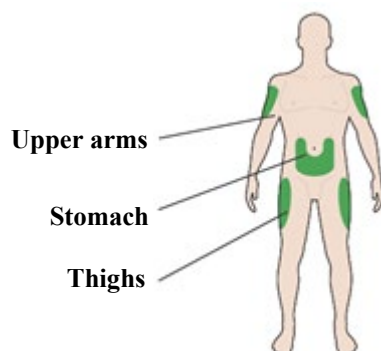
Need help?

If you have any questions about Soliqua, the pen or about diabetes, ask your doctor, pharmacist or nurse

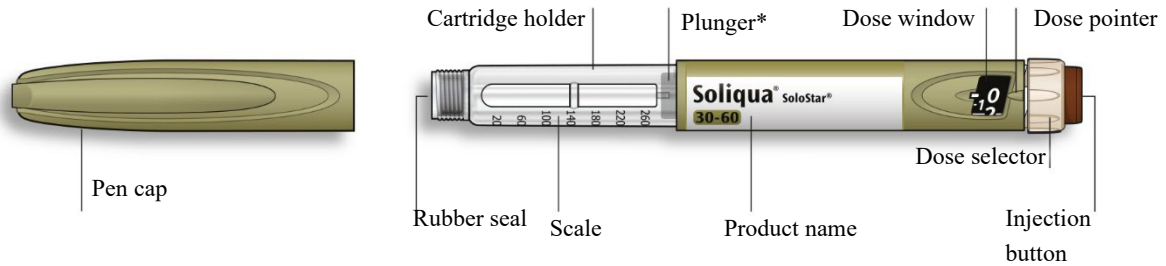
Additional items you will need:

- a new sterile needle (see **STEP 2**).
- a sharps container for used needles. (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

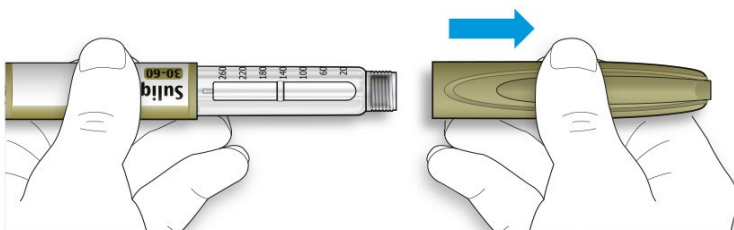
For first use of a new pen take it out of the refrigerator at least **1** hour before you inject. Injecting cold medicine is more painful. After first use the pen will be stored at temperatures below 25°C.

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

- Make sure you have the correct medicine. This pen is olive coloured with a brown injection button.
- **Do not use this pen if you need a daily dose less than 30 dose steps or if you need more than 60 dose steps. Discuss with your doctor which pen is suitable for your needs.**
- **Do not** use your pen after the expiry date.

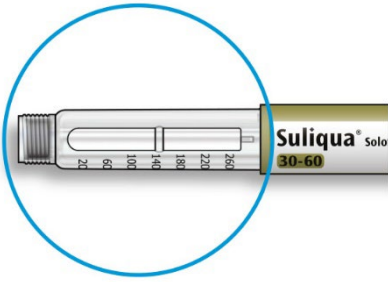


B. Pull off the pen cap.



C. Check that the medicine is clear.

- Look at the transparent cartridge holder. **Do not** use the pen if the medicine looks cloudy, coloured or contains particles.



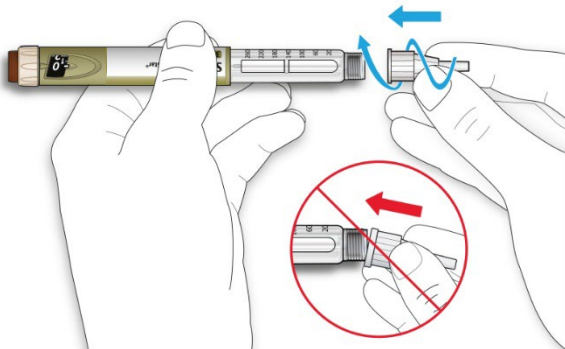
STEP 2: Attach a new needle

- **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.

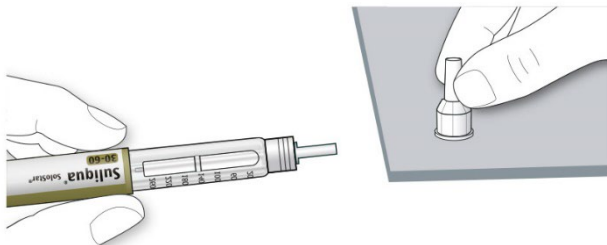
A. Take a new needle and peel off the protective seal.



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

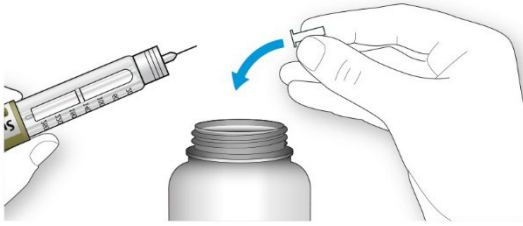


C. Pull off the outer needle cap. Keep this for later.



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

If you try to put it back on, you may accidentally stick yourself with the needle.



Handling needles

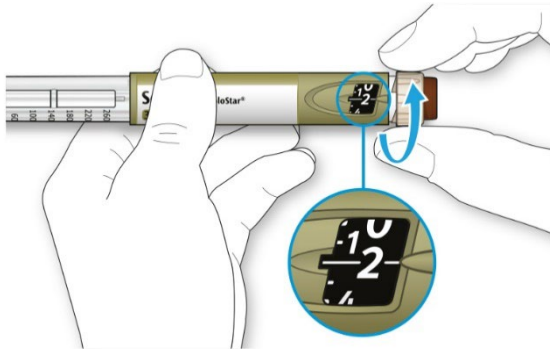
- Take care when handling needles to prevent needle injury and cross-infection.

STEP 3: Do a safety test

Always do a safety test before each injection to:

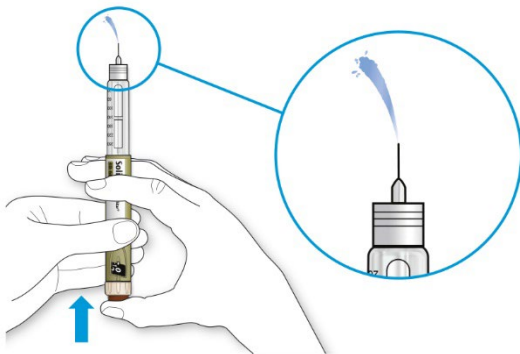
- Check your pen and the needle to make sure they are working properly
- Make sure that you get the correct dose.

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 30 to 60 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 30 dose steps. Always use another Soliqua (30- 60) Solostar pen to complete your dose and no other pen.

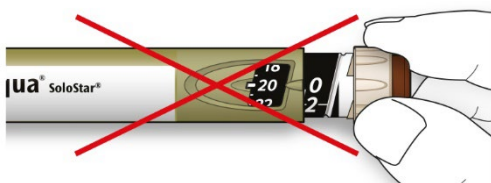
How to read the dose window

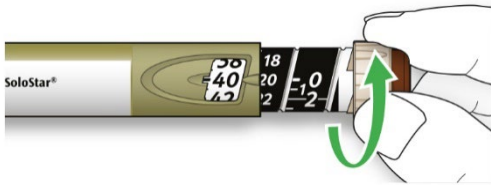
- Even numbers are presented in line with the dose pointer and odd numbers are presented as a line between even numbers.



39 units selected

- **Do not** use the pen if your single daily dose is less than 30 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 30 dose steps, or more than 60 dose steps. Discuss with your doctor which pen is suitable for your needs.
- Each pen contains more than 1 dose.

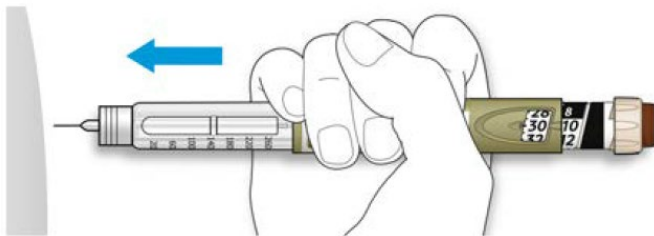
STEP 5: Inject the dose

- 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.

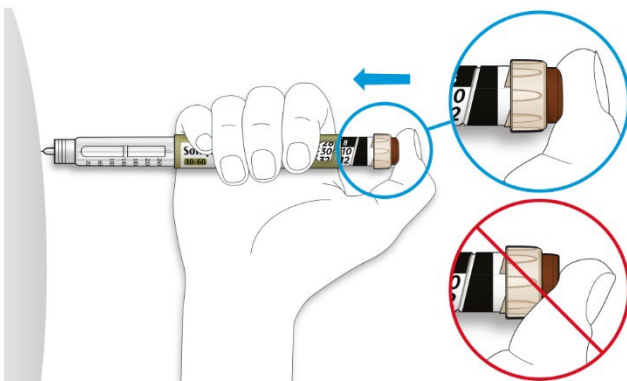
B. Push the needle into your skin as shown by your doctor or pharmacist or nurse.

- Do not touch the injection button yet.



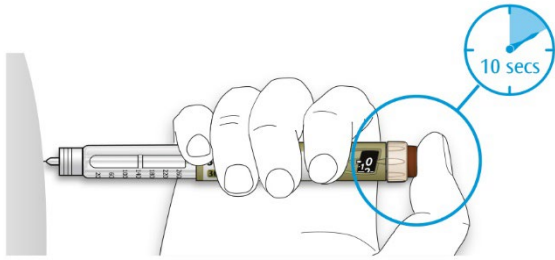
C. Place your thumb on the injection button. Then press all the way in and hold.

- **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.



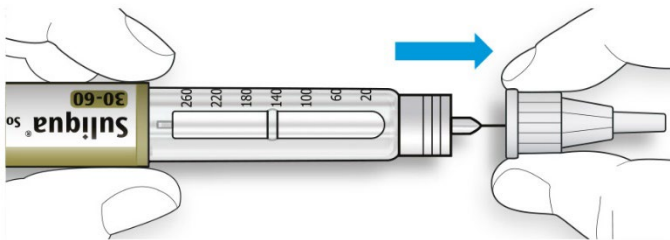
E. After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin.

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.

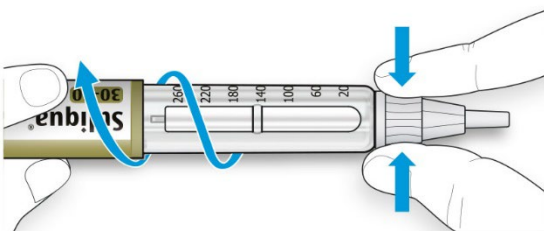
A. Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.

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

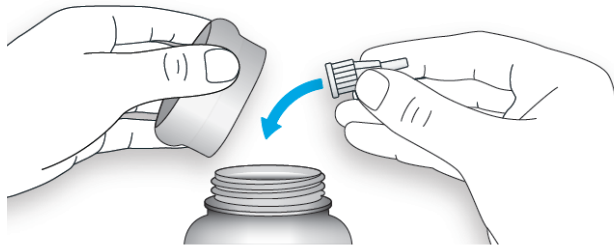


B. Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.

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

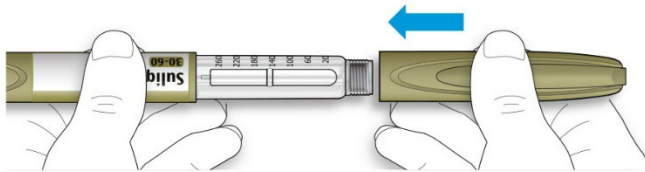


C. Throw away the used needle in a puncture resistant container (see “Throwing your pen away” at the end of this Instructions for Use).



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.