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

This package insert is continually updated: Please read carefully before using a new pack

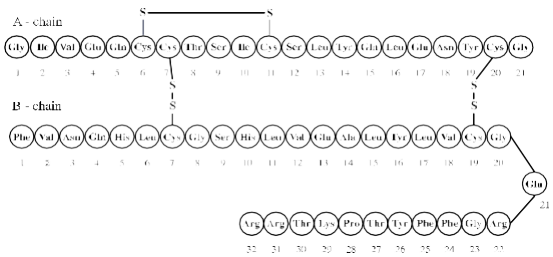
Fixed ratio combination of Insulin Glargine + Lixisenatide

Soliqua® SoloStar®

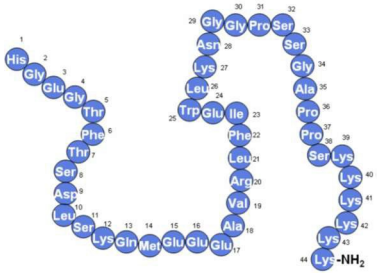
Active Ingredient

Insulin glargine
Recombinant human insulin analogue.
(21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin)
Insulin glargine is produced by recombinant DNA technology utilizing *Escherichia coli* (K12 strain) as the production organism.

Insulin glargine has the following structural formula:



Lixisenatide,
A peptide containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44). The order of the amino acids is given in the figure below. Its molecular weight is 4858.5, and the empirical formula is $C_{215}H_{347}N_{61}O_{65}S$ with the following chemical structure:



Lixisenatide is an amorphous, hygroscopic, white to off-white powder.

Therapeutic or Pharmacological Class
Antidiabetic

Indication:

Soliqua® is indicated for the treatment of adults patients with Obesity with insufficiently controlled type 2 diabetes mellitus to improve glycemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT2 inhibitors, when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product (sulfonylurea, glinide, DPP-4 inhibitors or gliptins, and Sodium-glucose co-transporter 2 (SGLT2) inhibitors or gliflozins) or with basal insulin or with glucagon-like peptide-1 (GLP-1) receptor agonist.

Pharmaceutical Form(s)
Soliqua® is available as a sterile solution for injection in prefilled pen in two dosage strengths:
Soliqua® 10-40 prefilled pen contains per mL 100 units insulin glargine and 50 mcg lixisenatide
Soliqua® 30-60 prefilled pen contains per mL 100 units insulin glargine and 33 mcg lixisenatide
The product will be administered parenterally (subcutaneously).

Composition
• Fixed ratio combination of Insulin Glargine 100U/ml +Lixisenatide 33mcg/ml
Each ml contains:
Insulin Glargine I.P. - 100 U(3.6378mg)
Lixisenatide - 0.033mg
m-Cresol - 2.7mg (as preservative)
Excipients - q.s.

• Fixed ratio combination of Insulin Glargine 100U/ml +Lixisenatide 50mcg/ml
Each ml contains:
Insulin Glargine I.P. - 100 U(3.6378mg)
Lixisenatide - 0.05mg
m-Cresol - 2.7mg (as preservative)
Excipients - q.s.

Dosage and Administration
Soliqua® is titratable and available in two pens, providing different dosing options. The differentiation between the pen strengths is based on the dose range of the pen:

- Soliqua® 100 units/mL and 50 mcg/mL: 10-40 pen
  - 1 unit of Soliqua® contains 1 unit of insulin glargine and 0.5 mcg lixisenatide
  - allows daily doses between 10 and 40 units of Soliqua® (10 to 40 units of insulin glargine in combination with 5 to 20 mcg lixisenatide).

- Soliqua® 100 units/mL and 33 mcg/mL: 30-60 pen
  -1 unit of Soliqua® contains 1 unit of insulin glargine and 0.33 mcg lixisenatide
  - allows daily doses between 30 and 60 units of Soliqua® (30 to 60 units insulin glargine/10 to 20 mcg lixisenatide).

  To avoid medication errors, make sure the correct Soliqua® pen, (10-40) pen or (30-60) pen, is stated in the prescription. The maximum daily dose of Soliqua® is 60 units of Soliqua® (60 units insulin glargine and 20 mcg lixisenatide).

Soliqua® should be administered subcutaneously once a day within 1 hour prior to any meal. It is preferable that the prandial injection of Soliqua® is performed before the same meal every day, when the most convenient meal has been chosen. If a dose of Soliqua® is missed, it should be injected within the hour prior to the next meal.

The dose of Soliqua® must be individualized 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.

Patients adjusting the amount or timing of dosing with Soliqua®, should only do so under medical guidance with appropriate glucose monitoring [see section Warnings and Precautions].

***Initiation* of Soliqua®**

Starting Dose of Soliqua®

Therapy with basal insulin or GLP-1 receptor agonist should be discontinued prior to initiation of Soliqua®. The starting dose of Soliqua® is selected based on previous anti-diabetic treatment and in order not to exceed the recommended lixisenatide starting dose of 10 mcg:.

Starting dose of Soliqua®

Previous treatment					
		Insulin naïve patients (Oral anti-diabetic treatment or GLP-1 receptor agonist)	**Insulin glargine (U100)** ** **<20 Units**	**Insulin glargine (U100)** ** **≥20 to <30 Units**	**Insulin glargine (U100)** ** **≥30 to ≤60 Units Units**
Starting dose and Pen	**Soliqua® (10-40) pen**	**10 Units (10 Units/5 mcg)***		**20 Units (20 Units/10 mcg)***	
	Soliqua® - (30 60) pen				**30 Units (30 Units/10 mcg) ***

* Units Insulin Glargine (100 Units/mL) / mcg Lixisenatide

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

- For twice daily basal insulin or Toujeo, the total daily dose previously taken should be reduced by 20% to choose the Soliqua® starting dose.
- For any other basal insulin the same rule as for insulin glargine (U100) should be applied.

***Dosage titration* of Soliqua®**

Soliqua® is to be dosed in accordance with the individual patient's needs for insulin. It is recommended to optimize glycemic control via dose adjustment based on fasting self-monitored plasma glucose. (see section Pharmacodynamics).

Close glucose monitoring is recommended during the initiation and in the following weeks.

- If the patient starts with the Soliqua® (10-40) pen, the dose may be titrated up to 40 units with this pen.
- For total daily doses >40 units/day switch to the Soliqua® (30-60) pen.
- If the patient starts with the Soliqua® (30-60) pen, the dose may be titrated up to 60 units with this pen.
- For total daily doses >60 units/day, do not use Soliqua®.

Administration
Administration is a subcutaneous injection in the abdomen, deltoid, or thigh. The rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered drugs or meal patterns.

The injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy and cutaneous amyloidosis (*see Adverse reactions).*

SPECIAL POPULATIONS
Children
The safety and effectiveness of Soliqua® in pediatric patients below the age of 18 years have not been established.

Elderly (≥65 years old)
Soliqua® can be used in elderly patients. The dose should be adjusted on an individual basis, based on glucose monitoring. The therapeutic experience in patients ≥75 years of age is limited.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of Soliqua® has not been studied. Lixisenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide. 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.

Renal impairment
There is no therapeutic experience with use of lixisenatide in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease and therefore, it is not recommended to use lixisenatide in these populations. In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. Frequent glucose monitoring and dose adjustment may be necessary for Soliqua® in patients with renal impairment.

CONTRAINDICATIONS
Soliqua® is contraindicated in patients with known hypersensitivity to lixisenatide, insulin glargine or to any of the inactive ingredients in the formulation.

WARNINGS/PRECAUTIONS
Use of Soliqua®
Soliqua® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
Soliqua® has not been studied in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, glinides and pioglitazone.

Risk of pancreatitis
Use of GLP-1 receptor agonists have 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, Soliqua® should not be restarted. Use with caution in patients with a history of pancreatitis.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycemic 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 hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered (see Section Adverse reactions)

Hypoglycemia
Hypoglycemia was the most frequently reported observed undesirable adverse reactions during treatment with Soliqua®**.** Hypoglycemia may occur if the dose of Soliqua® is higher than required. Factors increasing the susceptibility to hypoglycemia 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 Interactions).

The dose of Soliqua® must be individualized based on clinical response and is titrated based on the patient's need for insulin (see section Dosage and Administration).

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycemia.

Acute gallbladder disease
The use of GLP-1 receptor agonists has been associated with acute gallbladder disease. Acute gallbladder events such as cholelithiasis or cholecystitis have been reported in patients treated with lixisenatide although a causal relationship has not been established. Patients should be informed of the characteristic symptoms of acute gallbladder disease: upper abdominal pain, fever, nausea, vomiting, and jaundice. If cholelithiasis is suspected, gallbladder exams and follow up are indicated.

Use in patients with severe gastroparesis
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 Special Populations).

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 (see section Interactions).

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 hyper- or hypoglycemia.

INTERACTIONS
Interaction studies with Soliqua® have not been performed.
A number of substances affect glucose metabolism and may require dose adjustment of Soliqua®.

Insulin glargine
A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood glucose lowering effect and susceptibility to hypoglycemia:

Oral antidiabetic products, ACE inhibitors, salicylates, disopyramide; fibrates; fluoxetine, MAO inhibitors; pentoxifylline; propoxyphene; sulfonamide antibiotics.

The following are examples of substances that may reduce the blood glucose lowering effect:
Corticosteroids; danazol; diazoxide; diuretics; sympathomimetic agents (such as epinephrine, salbutamol, terbutaline); glucagon; isoniazid; phenothiazine derivates; somatropin; thyroid hormones; estrogens, progestogens (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine)

Beta-blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycemia.

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.

Lixisenatide
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.

Effect of Gastric Emptying on Oral Medications
Lixisenatide delays gastric emptying which may reduce the rate of absorption of orally administered medications. Use caution when co administering oral medications with a narrow therapeutic ratio or that require careful clinical monitoring. If such medications are to be administered with food, patients should be advised to take them with a meal or snack when lixisenatide is not administered.

Oral medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, should be administered at least 1 hour before or 11 hours after Soliqua® injection.

Paracetamol (Acetaminophen)
Paracetamol was used as a model medicinal product to evaluate the effect of lixisenatide on gastric emptying. Lixisenatide 10 mcg did not change the overall exposure (AUC) of acetaminophen following administration of a single dose of acetaminophen 1000 mg, whether before or after lixisenatide. No effects on acetaminophen Cmax and tmax were observed when acetaminophen was administered 1 hour before lixisenatide. When administered 1 or 4 hours after 10 mcg lixisenatide, C_{max} of acetaminophen was decreased by 29% and 31% respectively and median t_{max} was delayed by 2.0 and 1.75 hours, respectively. Based on these results, no dose adjustment for acetaminophen is required.

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.
Based on these results, no dose adjustment for oral contraceptives is required. It is recommended that oral contraceptives be administered at least 1 hour before or at least 11 hours after Soliqua® administration.

Atorvastatin
When lixisenatide 20 mcg and atorvastatin 40 mg were coadministered in the morning for 6 days, the exposure of 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 Soliqua®. However, because of the delay in t_{max}, patients taking atorvastatin should be advised to take atorvastatin at least 1 hour before or 11 hours after Soliqua® administration.

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 Normalized 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 Soliqua®.

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 Soliqua®.

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 Soliqua®.

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

The potential risk for humans is unknown. Soliqua® should not be used during pregnancy.

If a patient wishes to become pregnant, or pregnancy occurs, treatment with Soliqua® should be discontinued.

Animal studies, with lixisenatide or insulin glargine, do not indicate direct harmful effects on the pregnancy.

Insulin Glargine
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) with insulin glargine indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor foeto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity with insulin glargine.

Lixisenatide
Studies in animals have shown reproductive toxicity (see section Non clinical safety data).

LACTATION
It is unknown if Soliqua® is excreted in human milk. Because of lack of experience, Soliqua® should not be used during breastfeeding.

No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine as a peptide is digested into amino acids in the human gastrointestinal tract.

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

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
The patient's ability to concentrate and react may be impaired as a result of, for example, hypoglycemia or hyperglycemia 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 operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:
Very common 10 %; Common 1 and <10 %; Uncommon 0.1 and < 1%;
Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

Insulin glargine and lixisenatide
Summary of the safety profile
The Soliqua® phase 3 clinical studies included 834 patients treated with Soliqua®. An additional phase 3 clinical study included 255 patients treated with Soliqua®.

The most frequently reported undesirable adverse reactions during treatment with Soliqua® were hypoglycemia and gastrointestinal adverse reactions (see section 'Description of selected adverse reactions' below).

Tabulated list of adverse reactions

System Organ Class	Frequency of occurrence			
	Very common	**Common**	**Uncommon**	**Unknown**
Infections and Infestations			**Nasopharyngitis** **Upper respiratory tract infection**	
Immune system disorders			**Urticaria**	
Metabolism and nutrition disorders	**Hypoglycemia**			
Nervous system disorders		**Dizziness**	**Headache**	
Gastrointestinal disorders		**Nausea** **Diarrhea** **Vomiting**	**Dyspepsia** **Abdominal pain**	
General disorders and administration site conditions			**Fatigue** **Injection site reactions**	
Skin and subcutaneous tissue disorders				**Lipodystrophy** * **Cutaneous amyloidosis** *

* Adverse reaction observed for insulin glargine

Hypoglycemia
Severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Documented symptomatic or severe hypoglycemic 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 hypoglycemia* Patients with event, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)	146 (40.0)	155 (42.5)	71 (28%)	6 (23%)

Events per patient-year, n	1.44	1.22	0.34	3.03	4.22	1.54	0.08
Severe hypoglycemia** Events per patient-year, n	0	<0.01	0	0.02	<0.01	<0.01	0

* Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L).
** Severe symptomatic hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Gastrointestinal disorder

Gastrointestinal adverse reactions (nausea, vomiting and diarrhea) were frequently reported adverse reactions during the treatment period. After 30 weeks of treatment with Soliqua® in two pooled phase 3 trials, in patients treated with Soliqua®, the incidence of related nausea, diarrhea and vomiting was 8.4%, 2.2% and 2.2%, respectively. Gastrointestinal adverse reactions were mostly mild and transient in nature. 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. In patients treated with lixisenatide, the incidence of related nausea, diarrhoea and vomiting was 22.3%, 3% and 3.9%, respectively. In a third phase 3 trial, after 26 weeks of treatment, in patients treated with Soliqua® the incidence of related nausea, diarrhea and vomiting was 5.5%, 0.8%, and 1.2% respectively.

Skin and subcutaneous tissue disorders

Lipodystrophy*: Subcutaneous administration of injectable products containing insulin could result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) at the injection site.

Localized cutaneous amyloidosis* at the injection site has occurred with insulins. Hyperglycemia has been reported with repeated insulin injections into areas of cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

Continuous rotation of the injection site within the given injection area may help to reduce the risk or prevent these reactions (see Section Warnings/Precautions).

*Although localized cutaneous amyloidosis and lipodystrophy were not seen as related to insulin glargine + lixisenatide, these are known adverse reactions for all insulins including insulin glargine.

Immune system disorders

Allergic reactions (urticaria) possibly related with Soliqua® has been reported in 0.3% of patients[25]. Cases of generalised allergic reaction including anaphylactic reaction and angioedema have been reported during marketed use of insulin glargine and lixisenatide.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

Administration of Soliqua® may cause formation of antibodies against insulin glargine and/or lixisenatide.

After 30 weeks of treatment with Soliqua® in two phase 3 trials, 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. In a third phase 3 trial, after 26 weeks of treatment with Soliqua®, the incidence of formation of anti-insulin glargine antibodies was 17.4% and 44.5% for anti-lixisenatide antibodies.

Injection site reactions
Some patients taking insulin containing therapy, including Soliqua® have experienced erythema, local oedema, and pruritus at the site of injection. These conditions were usually self-limiting.

OVERDOSE

SIGNS AND SYMPTOMS

Limited clinical data are available with regard to overdose of Soliqua®.
Hypoglycemia and gastrointestinal adverse reactions may develop if a patient is dosed with more Soliqua® than required.

Insulin Glargine
An excess of insulin, relative to food intake, energy expenditure or both, may lead to severe and sometimes prolonged and life-threatening hypoglycemia.

Lixisenatide
During clinical studies, doses up to 60 µg of lixisenatide were administered to type 2 diabetic patients in a 13-week study. They were well tolerated and only an increased incidence of gastrointestinal disorders was observed.

MANAGEMENT

Insulin Glargine
Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes culminating in 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 hypoglycemia may recur after apparent clinical recovery.

Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and the Soliqua® dose should be reduced to the prescribed dose.

PHARMACODYNAMICS

Mechanism of Action

Soliqua®
Soliqua® combines 2 antihyperglycemic agents with complementary mechanisms of action: insulin glargine, a basal insulin analog, and lixisenatide, a GLP-1 receptor agonist, which targets fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) to improve glycemic control in patients with type 2 diabetes, while minimizing weight gain and risk for hypoglycemia.

Insulin Glargine
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs 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 glucagon-like peptide (GLP-1) receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas.

Similar to endogenous GLP-1, the action of lixisenatide is mediated via a specific interaction with GLP-1 receptors, including those on pancreatic alpha and beta cells. After a meal, lixisenatide activates the following individual physiologic responses:

- Enhances insulin secretion by β-cells
- Slows gastric emptying
- Suppresses glucagon secretion by α-cells

Lixisenatide stimulates glucose dependent insulin secretion. In parallel, glucagon secretion is suppressed.

Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose is absorbed and appears in the circulation. Lixisenatide has been shown to preserve beta cell function and prevent cell death (apoptosis) in isolated human pancreatic islet cells.

Pharmacodynamic Properties

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 utilization rate/time profile was similar, no pronounced peak, when given in the combination insulin glargine/lixisenatide.

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 assessing the effects of 5 to 20 mcg lixisenatide QD or BID doses of lixisenatide on blood glucose induced by a standardized breakfast test meal, 10 and 20 mcg QD or BID lixisenatide improved glycemic control through the effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes. Lixisenatide administered in this study in the morning at a dose of 20 mcg QD maintained statistically significant decreases in postprandial blood glucose after breakfast, lunch and dinner.

Postprandial glucose
In a 4-week treatment study in patients with type 2 diabetes in combination with metformin and in an 8-week treatment study in combination with insulin glargine with or without metformin, lixisenatide 20 mcg once daily administered before breakfast, demonstrated reduction of postprandial plasma glucose (AUC 0:30-4:30h) after a test meal. The number of patients with 2h post prandial glucose levels below 140 mg/dL {7.77 mmol/L} was 69.3% after 28 days and 76.1% after 56 days.

Insulin secretion
In a monotherapy study, lixisenatide alone restores the first-phase insulin secretion in patients with type 2 diabetes in a glucose-dependent manner by 2.8-fold (90% CI, 2.5-3.1) and increases the second-phase insulin secretion by 1.6-fold (90% CI, 1.4-1.7) compared with placebo as measured by AUC.

Gastric emptying
Following a standardized labeled test meal, lixisenatide slows gastric emptying, thereby reducing the rate of postprandial glucose absorption. Following 28-day treatment with lixisenatide alone the slowing effect of gastric emptying is maintained in patients with type 2 diabetes.

Glucagon secretion
Lixisenatide 20 mcg once daily alone demonstrated decreased postprandial glucagon levels versus baseline after a test meal in patients with type 2 diabetes. In a placebo-controlled hypoglycemic clamp study in healthy subjects assessing the effect of single injection of 20 mcg lixisenatide on glucagon response, counter-regulatory glucagon response was preserved under hypoglycemic conditions in the presence of effective lixisenatide plasma concentrations.

Cardiac electrophysiology (QTc)
The effect of lixisenatide on cardiac repolarization was tested in a QTc study (at 1.5 times the approved maintenance dose) which indicated no relevant impact of lixisenatide on ventricular repolarization.

Heart Rate
No increase in mean heart rate was seen in Soliqua® phase 3 placebo-controlled studies.

PHARMACOKINETICS

Soliqua®
The insulin glargine/lixisenatide ratio has no relevant impact on the PK of insulin glargine in Soliqua®. Compared to administration of lixisenatide alone, the C_{max} is lower whereas the AUC is generally comparable when administered as Soliqua®. The observed differences in the PK of lixisenatide when given as Soliqua® or alone are not considered to be clinically relevant.

ABSORPTION

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 ranged from 86% to 101% compared to administration of insulin glargine alone.

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. 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 is administered subcutaneously in the abdomen, thigh, or arm.

DISTRIBUTION
Lixisenatide
Lixisenatide has a moderate level of binding (55%) to human proteins.

METABOLISM AND ELIMINATION
Insulin Glargine
A metabolism study in humans who received insulin glargine alone indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of human insulin, M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Lixisenatide

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.

SPECIAL POPULATIONS

Age, Race, and Gender.

Insulin glargine

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

Lixisenatide

Based on the population PK analysis, age, body weight, gender, and race do not have a clinically meaningful effect on pharmacokinetics of lixisenatide.

Obesity

Effect of Body Mass Index (BMI) on the pharmacokinetics of Soliqua® has not been evaluated.

Hepatic Impairment

Lixisenatide

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.

Renal Impairment

A single-dose, open-label study evaluated the pharmacokinetics of lixisenatide 5 mcg in subjects with varying degrees of renal impairment (classified using the Cockcroft-Gault formula for Creatine Clearance (CLcr)) compared to healthy subjects.

There were no relevant differences in mean C_{max} and AUC of lixisenatide between subjects with normal renal function and subjects with mild impaired renal function (CLcr 60-90 ml/min). In subjects with moderate renal impairment (CLcr 30-60 ml/min) AUC was increased by approximately 51% and in subjects with severe renal impairment (CLcr 15-30 ml/min) AUC was increased by approximately 87%.

CLINICAL EFFICACY/CLINICAL STUDIES

Overview of Clinical Studies

The safety and effectiveness of Soliqua® on glycemic control were evaluated in three randomized clinical studies in patients with type 2 diabetes mellitus:

- Add-on to Oral Anti-diabetics (OADs) [insulin naïve]
- Switch from basal insulin
- Switch from GLP-1 receptor agonist

In each of the active controlled trials, treatment with Soliqua® produced clinically and statistically significant improvements in haemoglobin A1c (HbA1c).

Reaching lower HbA1c levels and achieving greater HbA1c reduction did not increase rates of hypoglycemia with combination treatment versus insulin glargine alone [see section Adverse Reactions]

In the add-on to metformin clinical study the starting dose was 10 units. In the switch from basal insulin clinical study the starting dose was 20 or 30 units depending on the previous insulin dose. In both studies

the dose was titrated once weekly, based on median fasting self-measured plasma glucose values from the preceding 3 days according to Table 4 below.

Table 4 – Dose adjustment algorithm Soliqua®

Fasting self-measured plasma glucose (mg/dl) {mmol/L}	Dose change (units/day)
>140 {>7.77}	+4
>100 and ≤140 {>5.55 and ≤7.77}	+2
80 to 100 {4.44 to 5.55}	No change
<80 {<4.44}	-2

Clinical Study in Patients with Type 2 Diabetes Uncontrolled on OAD treatment
Add-on to Oral Anti-diabetics (OAD) [Insulin Naïve]
A total of 1170 patients with type 2 diabetes were randomized 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.

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% to10% 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 optimized 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 randomized to either Soliqua®, insulin glargine or lixisenatide. In total 58% of patients at screening received a second OAD.

The type 2 diabetes population had the following characteristics: Mean age was 58.4 years, 50.6 percent were male, 90.1% were Caucasian, 6.7 % were Black or African American and 19.1 % were Hispanic. The mean BMI at baseline was 31.7 kg/m2. The mean duration of diabetes was approximately 9 years.

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 5 and Figure 2 for the other endpoints in the study.

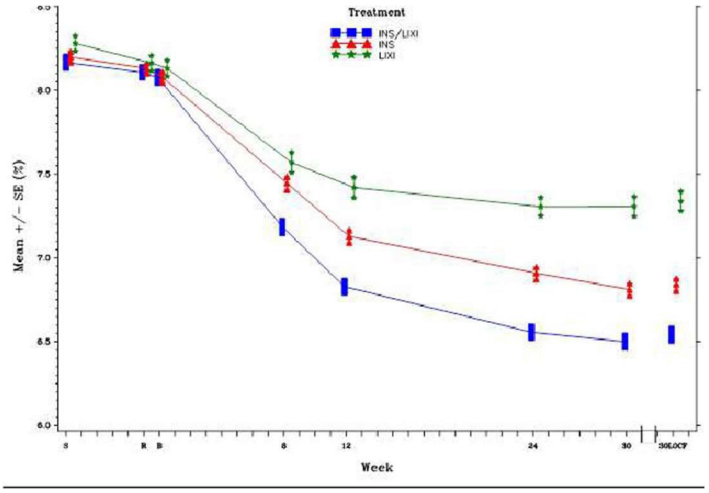
Table 5: Results at 30 weeks - Add-on to metformin clinical study (mITT population)

	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.
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 (mg/dL) {mmol/L}			
Baseline (mean)	178.0 {9.88}	175.7 {9.75}	176.4 {9.79}
End of study (mean)	113.9 {6.32}	117.6 {6.53}	148.9 {8.27 }
LS change from baseline (mean)	-62.4 {-3.46}	-59.0 {-3.27}	-27.0 {-1.50}
LS difference versus glargine (mean) [95%CI] (p-value)		-3.5 [-7.6 to 0.7] {-0.19 [-0.420 to 0.038]} (0.1017)	
LS difference versus lixisenatide (mean) [95% CI] (p-value)			-35.4 [-40.5 to -30.3] {-1.96 [-2.246 to -1.682]} (<0.0001)
2 hour PPG (mg/dL){mmol/L} [2 hr Glucose excursion* (mg/dL) {mmol/L}]			
LS change from baseline to week 30 (mean)	-102.4 {-5.68} [-44.9 {-2.31}]	-59.6 {-3.31} [-3.9 {-0.18}]	-82.62 {-4.58} [-60.6 {-3.23}]
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

*2 hr PPG minus the pre-meal glucose value

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



*LOCF = Last observation carried forward.

Patients in the Soliqua® group reported a statistically significantly greater decrease in the average 7 point SMPG profile from baseline to Week 30 (-60.36 mg/dL {-3.35 mmol/L}) compared to patients in the insulin glargine group (-47.87 mg/dL {-2.66 mmol/L}); difference 12.49 mg/dL{-0.69 mmol/L}) and patients in the lixisenatide group (-35.11 mg/dL; difference 25.24 mg/dL) {(-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.

Studies in Patients with Type 2 Diabetes Uncontrolled on Basal Insulin

Switch from Basal Insulin

A total of 736 patients with type 2 diabetes participated in a randomized, 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 units 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% and a FPG less than or equal to 180mg/dL {9.99 mmol/L} or 200mg/dL {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 were switched to insulin glargine, in case they took another basal insulin, and had their insulin dose titrated/stabilized 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 ≤140 mg/dL {7.77 mmol/L} and insulin glargine daily dose of 20 to 50 units, were randomized to either *TM* (n=367) or insulin glargine (n=369).

This type 2 diabetes population had the following characteristics: Mean age was 60 years, 46.7 percent were male, 91.7% were Caucasian, 5.2 % were Black or African American and 17.9 % were Hispanic.

The mean BMI at screening was approximately 31 kg/m^2.
The mean duration of diabetes was approximately 12 years.

At Week 30, Soliqua® provided statistically significant improvement in HbA1c (p-value <0.0001) compared to insulin glargine.

See Table 6 and Figure 3 for the other endpoints in the study.

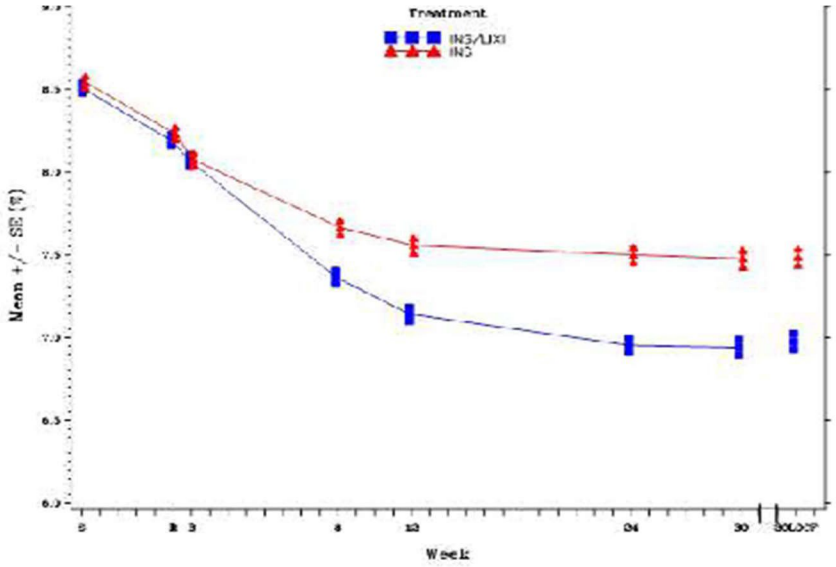
Table 6: Results at 30 weeks -Study Type 2 Diabetes Uncontrolled on Basal Insulin mITT population

	Soliqua®	**Insulin Glargine**
Number of subjects (mITT)	366	365
HbA1c (%)		
At screening (mean)	8.5	8.5
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 (mg/dL) {mmol/L}		
Baseline (mean)	132.0 {7.33}	132.0 {7.32}
End of study (mean)	122.1 {6.78}	120.5 {6.69}
LS change from baseline (mean)	-6.3 {-0.35}	-8.3 {-0.47}
2hour PPG (mg/dL{mmol/L}) [2 hr Glucose excursion* (mg/dL) {mmol/L}]		
LS change from baseline to week 30 (mean)	-85.1 {-4.72} [-70.2 {-3.90}]	-25.1 {-1.39 [-8.4 {-0.47}]
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

*2 hr PPG minus the pre-meal glucose value

Figure 3 - Mean HbA1c (%) during 30 week randomized treatment period mITT population



*LOCF = Last observation carried forward

Clinical Studies in Patients with Type 2 Diabetes Uncontrolled on GLP-1 receptor agonist

Switch from 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 ≥60 mL/min.
The starting dose of Soliqua® was 10 units (10 units insulin glargine/5 mcg lixisenatide). The mean dose at baseline was 1.7 mg for liraglutide, 18.2 mcg for exenatide, 1.4 mg for dulaglutide, 2 mg for exenatide extended release, and 47.8 mg for albiglutide.
Soliqua® was titrated twice weekly during the first 8 weeks of treatment to target a fasting self-measured plasma glucose (SMPG) goal of 80 to 100 mg/dL. Thereafter, the dose was adjusted as necessary to maintain this fasting SMPG target, with recommendation to evaluate the dose at least once a week. The mean daily dose of Soliqua® at Week 26 was 43.5 units.
The primary endpoint, change in HbA1c at week 26, was tested for superiority of Soliqua® to unchanged GLP-1 receptor agonist therapy. At week 26, there was a reduction in HbA1c from baseline of -1.0% for Soliqua® and -0.4% for GLP-1 receptor agonist. The mean difference (95% CI) in HbA1c reduction between Soliqua® and GLP-1 receptor agonist was -0.6 [-0.80, -0.5] and was statistically significant.
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 highly consistent with the primary analysis for the overall population.
See table and figure below for the other endpoints in the study.

Table 7: Results at 26 weeks - Study Type 2 Diabetes Uncontrolled on GLP-1 receptor agonist mITT population

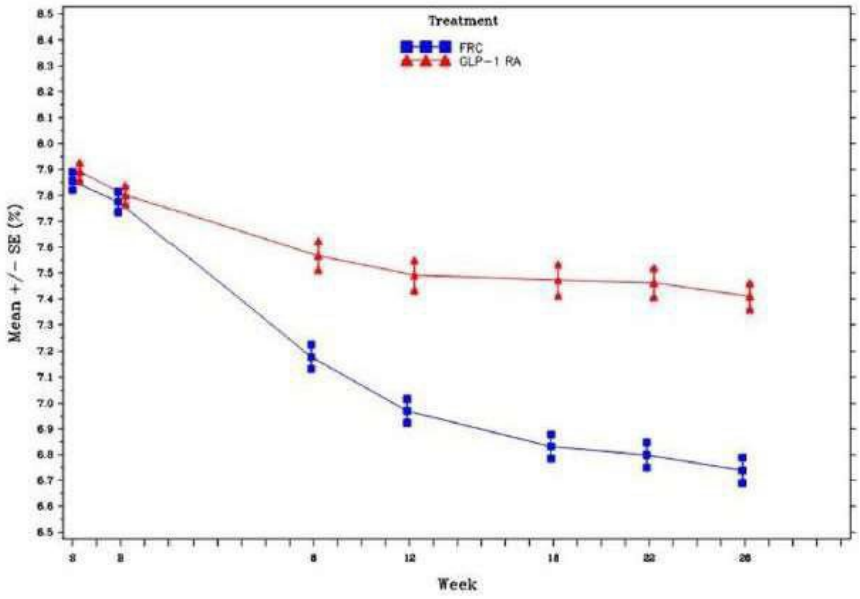
	Soliqua®	**GLP-1 receptor agonist**
Number of subjects (mITT)	252	253
HbA1c (%)		
Baseline (mean)	7.8	7.8
End of treatment (mean)	6.7	7.4
LS change from baseline (mean)	-1.0	-0.4
Difference versus GLP-1 receptor agonist [95% confidence interval] (p-value)	-0.6 [-0.8, -0.5] (<0.0001)	
Patients [n (%)] reaching HbA1c <7% at week 26	156 (61.9%)	65 (25.7%)
Proportion difference (95% CI) vs. GLP-1 receptor agonist	36.1 (28.1% to 44.0%)	
p-value	<.0001	
Fasting Plasma glucose (mg/dL) {mmol/L}		
Baseline (mean)	163.2 {9.06}	170.2 {9.45}
End of study (mean)	123.6 {6.86}	156.1 {8.66}
LS change from baseline (mean)	-41.0 {-2.28}	-10.9 {-0.60}
Difference versus GLP-1 receptor agonist [95% confidence interval] (p-value)	-1.67 {-2.00 to -1.34} (<0.0001)	
Average 7-point SMPG (mmol/L)		
Baseline (mean)	9.41	9.53
End of study (mean)	7.70	8.79
LS change from baseline (mean)	-1.69	-0.67

LS difference versus GLP-1 receptor agonist (mean) [95% confidence interval] (p-value)	-1.02 (-1.325 to -0.708) (<0.0001)	
2 hour PPG (mg/dL{mmol/L})* [2 hr Glucose excursion* (mg/dL) {mmol/L}]		
LS mean change from baseline to week 26	-71.3 {-4.0} [-27.2 {-1.5}]	-20.0 {-1.1} [-9.4 {-0.5}]
LS mean difference vs GLP-1 receptor agonist	-51.3 {-2.9} [-17.8{-1.0}]	
Mean body weight (kg)		
Baseline (mean)	93.01	95.49
LS change from baseline (mean)	1.9	-1.1
Comparison versus GLP-1 receptor agonist [95% confidence interval]	3.0 [2.4 to 3.6]	
Insulin glargine daily dose (U)**		
Baseline (mean)	10.1	NA
Endpoint (mean)	43.5	NA

*2 hr PPG minus the pre-meal glucose value

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

Figure 4 - Mean HbA1c (%) by visit during 26-week randomization treatment period-mITT population



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, randomized, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The incidence of MACE was similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)].

In the ORIGIN trial, the overall incidence of cancer (all types combined) [Hazard Ratio (95% CI); 0.99 (0.88, 1.11)] or death from cancer [Hazard Ratio (95% CI); 0.94 (0.77, 1.15)] was also similar between treatment groups.

Lixisenatide
ELIXA study was a randomized, 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 positively adjudicated by the Cardiovascular Events Adjudication Committee: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. CV secondary endpoints included a composite of the primary endpoint, or hospitalization for heart failure or coronary revascularization. Changes in urinary albumin/creatinine ration (UACR) at 108 weeks were also a pre-specified secondary endpoint.

Median treatment duration was 22.4 months in the lixisenatide group and 23.3 months in the placebo group, and the median duration of study follow-up was 25.8 and 25.7 months; respectively. Mean HbA1c (±SD) in the lixisenatide and placebo groups was 7.72 (±1.32)% and 7.64 (±1.28)% at baseline and 7.46 (±1.51)% and 7.61 (±1.48)% at 24 months, respectively.

The incidence of the primary endpoint was similar in the lixisenatide and placebo 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. Similar percentages between treatments were also observed for the secondary endpoints, and for all the individual components of the composite endpoints. The percentages of patients hospitalized for heart failure were 4.0% and 4.2% in the lixisenatide and placebo group, respectively (HR [95% CI] = 0.96 [0.75 – 1.23]).

A smaller increase in UACR from baseline to Week 108 was observed in lixisenatide compared to placebo: -10.04% ± 3.53%; 95% CI = -16.95%, -3.13%.

NON-CLINICAL SAFETY DATA
No animal studies have been conducted with the combination of insulin glargine and lixisenatide to evaluate, carcinogenesis, mutagenesis, or impairment of fertility.

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

Lixisenatide
In 2-year subcutaneous carcinogenicity studies, non-lethal C-cell thyroid tumors were seen in rats and mice and are considered to be caused by a non-genotoxic GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. C-cell hyperplasia and adenoma were seen at all doses in rats and a no observed adverse effect level (NOAEL) could be not defined. In mice, these effects occurred at exposure ratio above 9.3-fold when compared to human exposure at the therapeutic dose. No C-cell carcinoma was observed in

mice and C-cell carcinoma occurred in rats with an exposure ratio relative to exposure at human therapeutic dose of about 900-fold. 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.

SHELF-LIFE
Refer outer carton
Shelf-life after first use of the pen: 28 days

STORAGE CONDITIONS
Unopened 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.

Opened 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.

PREPARATION AND HANDLING
Inspect Soliqua® before each use. Soliqua® must only be used if the solution is clear, colourless, with no particles visible. Since Soliqua® is a solution, it does not require resuspension before use.
Before first use, the pen must be stored at room temperature for 1 to 2 hours.

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 antidiabetic medicinal products, including the 2 different pens of Soliqua® Before using Soliqua®, the instructions for use included in the package leaflet must be read carefully.

Manufactured by: M/s Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

Importer: Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, Vadape. Tal: Bhiwandi - 16(Thane Z5) Pin :421302

Marketed by: Sanofi India Ltd., CTS NO. 117-B, L&T Business Park, Saki Vihar road, Powai. Mumbai-400072.

New drug permission no.: IMP/BIO/23/000016 dated 21-Feb 2023

Updated: Jan 2023

Source: Insulin Glargine + Lixisenatide CCDS v6 dated 29th Sept 2022

Soliqua® SoloStar ® solution for injection in a pre-filled pen

INSTRUCTIONS FOR USE

Soliqua® SoloStar® contains insulin glargine and lixisenatide combination in a fixed ratio.

The drug combination in this pen is for the daily injection of 10 to 40 / 30 to 60 units of insulin glargine and 5 to 20 / 10 to 20 micrograms of lixisenatide.

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

Keep this leaflet 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.
- Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject:

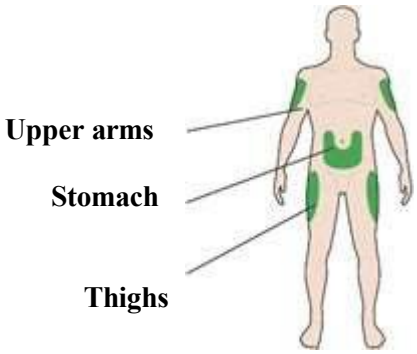
- Talk with your healthcare provider about how to inject, before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get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

If you have any questions about your pen or about diabetes, ask your healthcare provider.

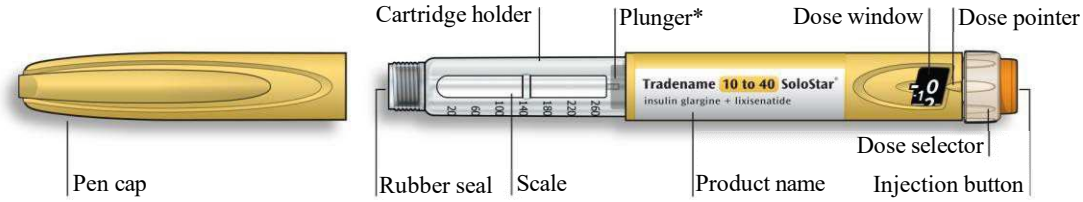
Extra items you will need:

- a new sterile needle (see **STEP 2**).
- an alcohol swab.
- a puncture resistant container for used needles and pens. (see **Throwing your pen away**)

Places to inject



Get to know your pen



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

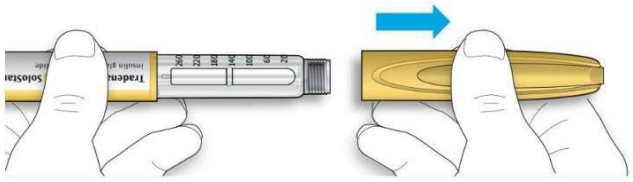
STEP 1: Check your pen

Take a new pen out of the refrigerator at least **1** hour before you inject. Cold medication is more painful to inject.

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

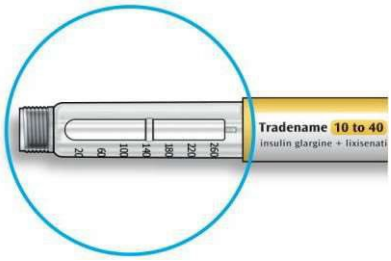
- Make sure you have the correct medication. This pen is peach colored with an orange injection button.
- **Do not use this pen if you need a daily dose less than 10 units or greater than 40 units. Discuss with your doctor which pen is suitable for your needs.**
- **Do not** use your pen after the expiration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

B. Pull off the pen cap.

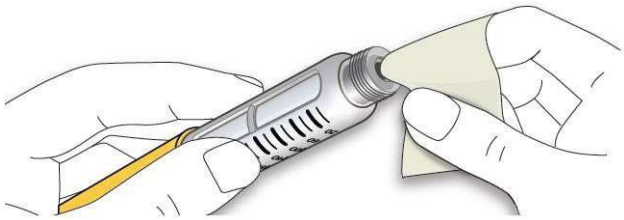


C. Check that the medication is clear.

- **Do not** use the pen if the medication looks cloudy, colored or contains particles.



D. Wipe the rubber seal with an alcohol swab.



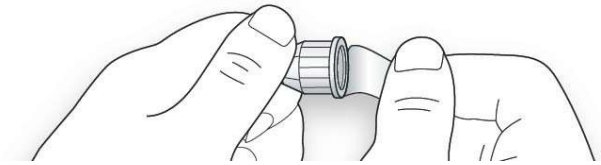
If you have other injector pens

- Making sure you have the correct medication is especially important if you have other injector pens.

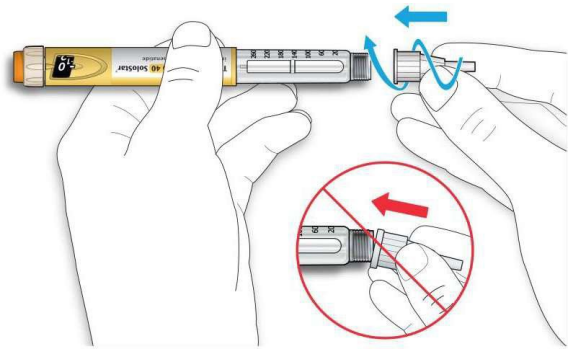
STEP 2: Attach a new needle

- **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® Solostar®, e.g. needles from BD, Ypsomed, Owen Mumford and Artsana.

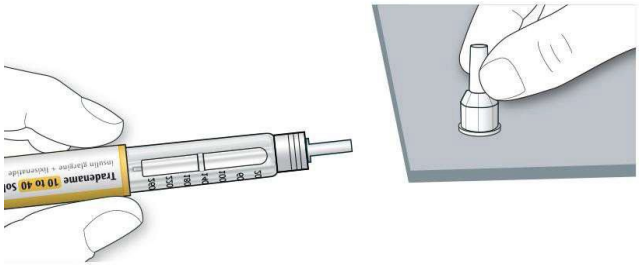
A. Take a new needle and peel off the protective seal.



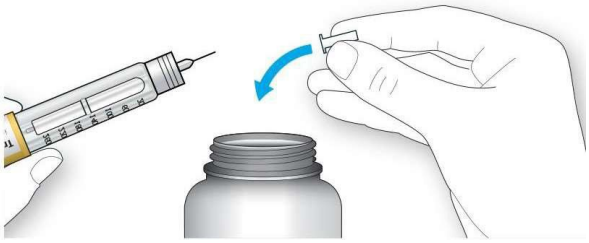
B. Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



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



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



Handling needles

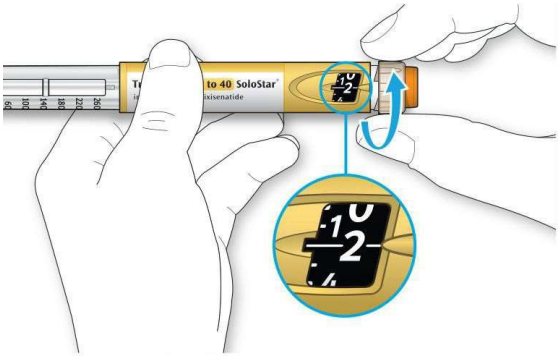
- Take care when handling needles to prevent needle injury and cross-infection.

STEP 3: Do a safety test

Always do a safety test before each injection to:

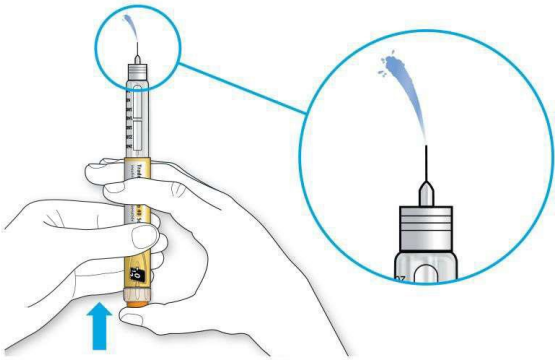
- Check your pen and the needle to make sure they are working properly
- Make sure that you get the correct dose.

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



B. Press the injection button all the way in.

- When medication comes out of the needle tip, your pen is working correctly.



If no liquid appears:

- You may need to repeat this step up to 3 times before seeing medication.
- If no medication 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 medication coming out of the needle tip. Use a new pen.
- **Do not** use a syringe to remove medication from your pen.

If you see air bubbles

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

STEP 4: Select the dose

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

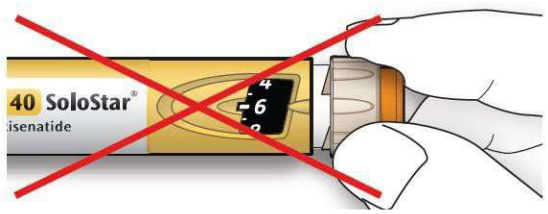
A. Make sure a needle is attached and the dose is set to '0'.

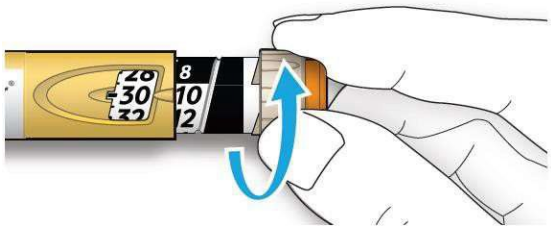
B. Turn the dose selector until the dose pointer lines up with your dose.

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

How to read the dose window

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





Units of medication in your pen

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

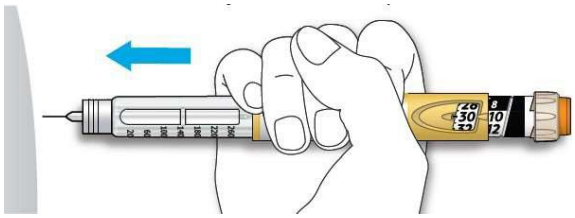
STEP 5: Inject the dose

- If you find it hard to press the injection button in, **do not** force it as this may break your pen. See section at the end of Step 5 for help.

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

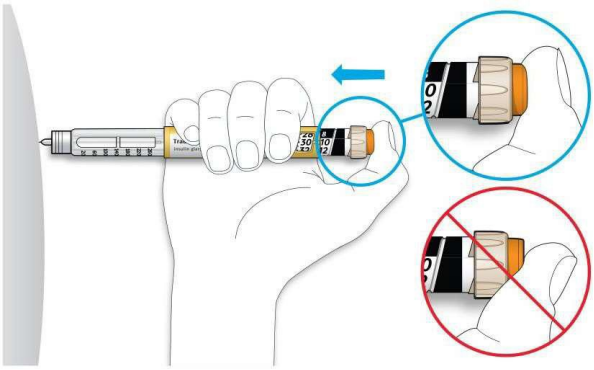
B. Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



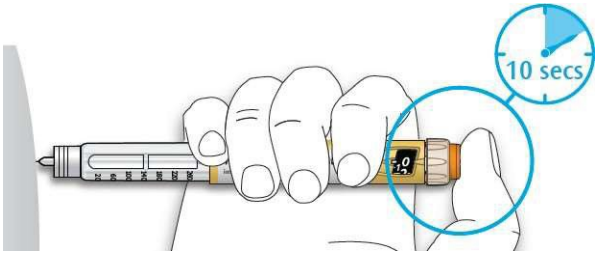
C. Place your thumb on the injection button. Then press all the way in and hold.

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



D. Keep the injection button held in and when you see "0" in the dose window, slowly count to10.

- 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.

If you find it hard to press the injection button in:

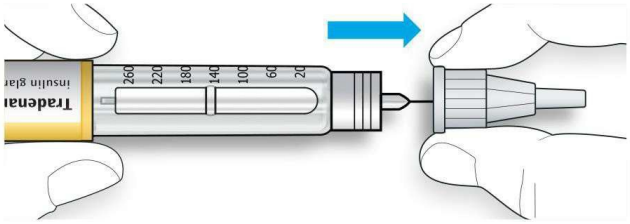
- Change the needle (**see STEP 6 and STEP 2**) then do a safety test (**see STEP 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove medication from your pen.

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.

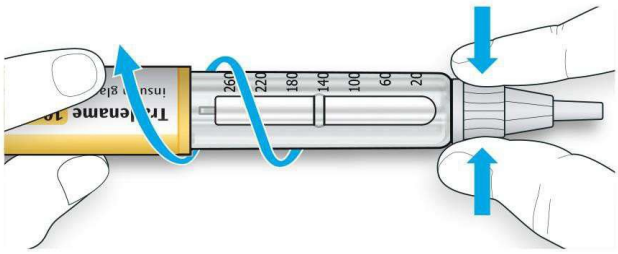
A. Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.

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

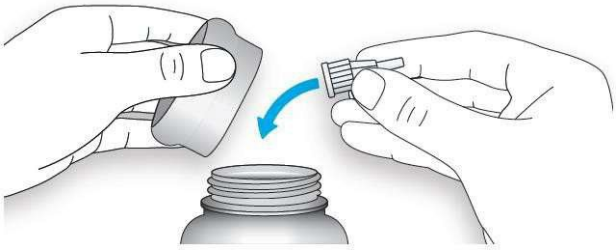


B. **Grip and squeeze the widest part of the outer needle cap.** Turn your pen several times with your other hand to remove the needle.

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

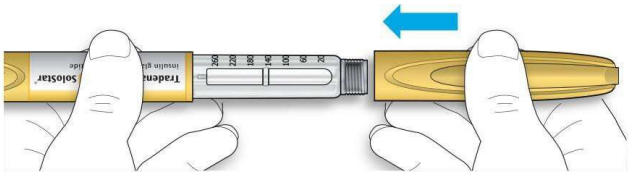


C. **Throw away the used needle in a puncture resistant container** (see "**Throwing your pen away**" at the end of this Instructions for Use).



D. **Put your pen cap back on.**

- Do not put the pen back in the refrigerator.



Use by

- Only use your pen for up to **28 days** after its first use.

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** for 28 days
- **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.

How to care for your pen Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- 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 told by your pharmacist or local authority.

Manufactured by: M/s Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

Importer: Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, Vadape. Tal: Bhiwandi - 16(Thane Z5) Pin :421302

Marketed by: Sanofi India Ltd., CTS NO. 117-B, L&T Business park, Saki Vihar road, Powai. Mumbai- 400072.

New drug permission no.: IMP/BIO/23/000016 dated 21-Feb 2023

Updated: Jan 2023

Source: Insulin Glargine + Lixisenatide CCDM V2 dated 22nd July 2021

Soliqua® SoloStar ® solution for injection in a pre-filled pen

INSTRUCTIONS FOR USE

Soliqua® SoloStar® contains insulin glargine and lixisenatide combination in a fixed ratio.

The drug combination in this pen is for the daily injection of 10 to 40 / 30 to 60 units of insulin glargine and 5 to 20 / 10 to 20 micrograms of lixisenatide.

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

Keep this leaflet 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.
- Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject:

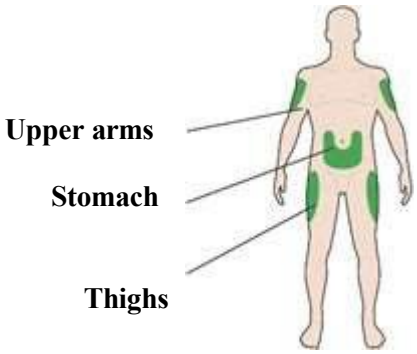
- Talk with your healthcare provider about how to inject, before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get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

If you have any questions about your pen or about diabetes, ask your healthcare provider.

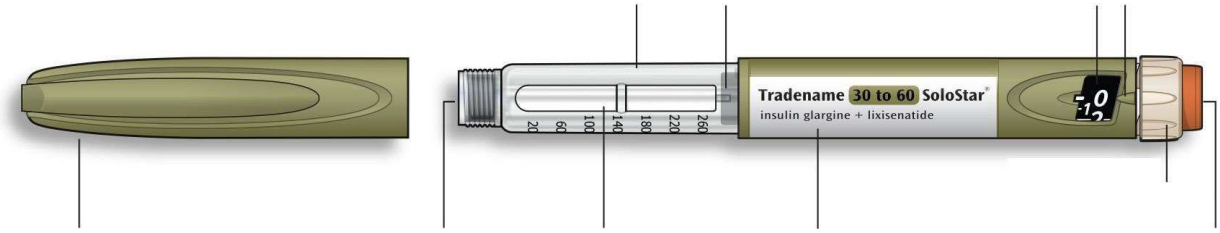
Extra items you will need:

- a new sterile needle (see **STEP 2**).
- an alcohol swab.
- a puncture resistant container for used needles and pens. (see **Throwing your pen away**).

Places to inject



Get to know your pen



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

STEP 1: Check your pen

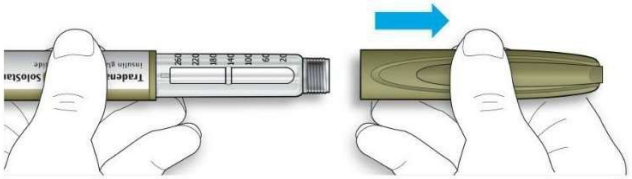
Take a new pen out of the refrigerator at least **1** hour before you inject. Cold medication is more painful to inject.

Step 1A:

Check the name and expiration date on the label of your pen.

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

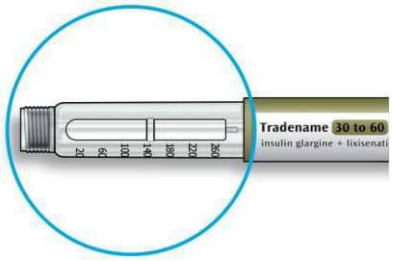
Step 1B:
Pull off the pen cap



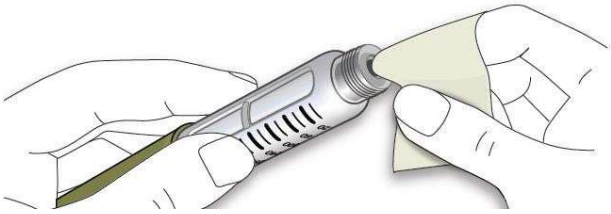
Step 1C:

Check that the medication is clear.

- **Do not** use the pen if the medication looks cloudy, colored or contains particles.



Step 1D: Wipe the rubber seal with an alcohol swab



If you have other injector pens

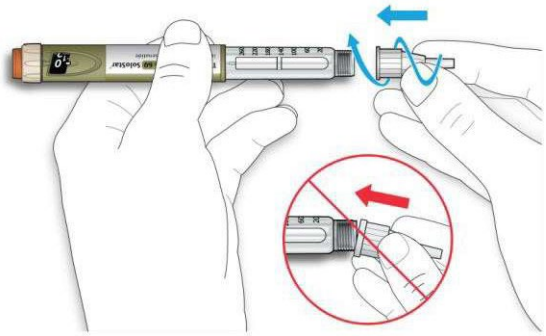
- Making sure you have the correct medication is especially important if you have other injector pens.

STEP 2: Attach a new needle

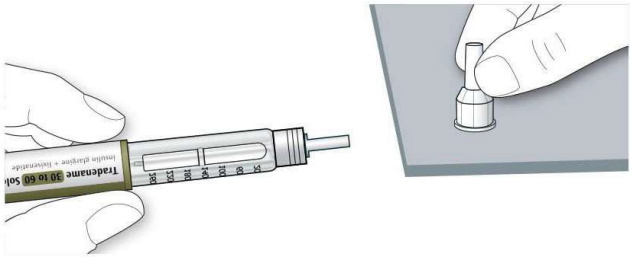
- **Do not** reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination, and infection.
- Always use needles that are compatible for use with Soliqua® SoloStar®, e.g. needles from BD, Ypsomed, Owen Mumford and Artsana.

Step 2A: Take a new needle and peel off the protective seal.

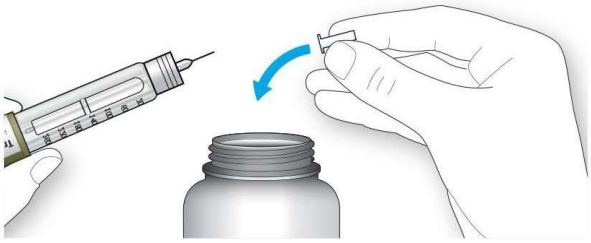
Step 2B: Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



Step 2C: Pull off the outer needle cap. Keep this for later



Step 2D: Pull off the inner needle cap and throw away



Handling needles

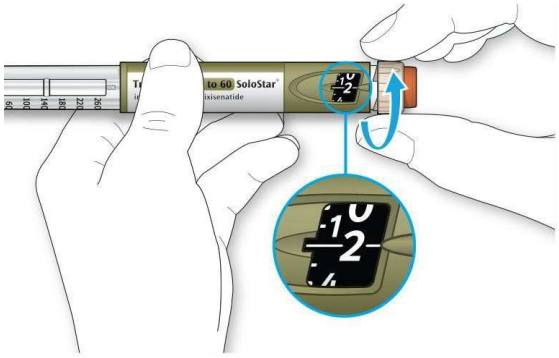
- Take care when handling needles to prevent needle injury and cross-infection.

STEP 3: Do a safety test

Always do a safety test before each injection to:

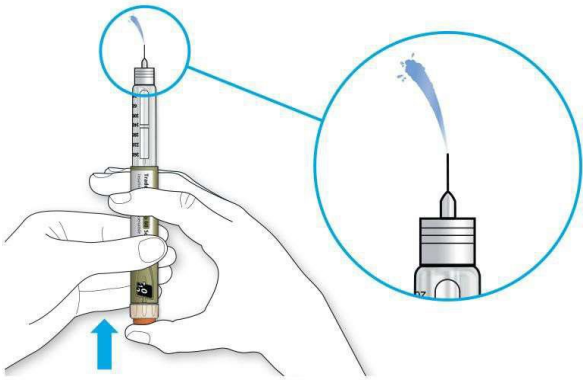
- Check your pen and the needle to make sure they are working properly
- Make sure that you get the correct dose.

Step 3A: Select 2 units by turning the dosage selector until the dose pointer is at the 2 mark



Step 3B: Press the injection button all the way in

- When medication comes out of the needle tip, your pen is working correctly.



If no liquid appears:

- You may need to repeat this step up to 3 times before seeing medication.
- If no medication 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 medication coming out of the needle tip. Use a new pen.
- **Do not** use a syringe to remove medication from your pen.

If you see air bubbles

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

STEP 4: Select the dose

- **Only use this pen to inject single daily doses from 30 to 60 units.**
- **Do not** select a dose or press the injection button without a needle attached. This may damage your pen.

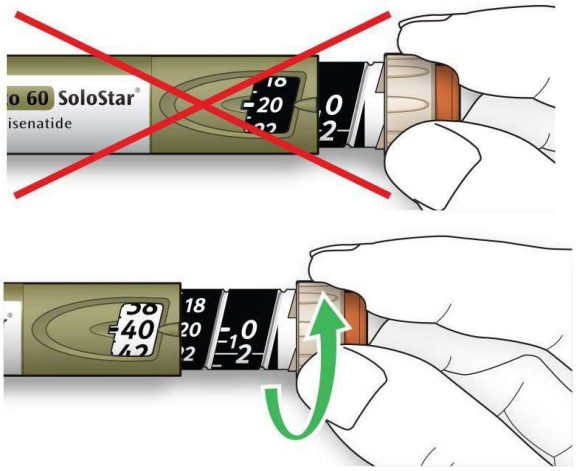
Step 4A: Make sure a needle is attached and the dose is set to '0'.

Step 4B: 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 units left in your pen for your dose, the dose selector will stop at the number of units left.
- If you cannot select your full prescribed dose, use a new pen or inject the remaining units and use a new pen to complete your dose. Only in this case, it is okay to inject a partial dose of less than 10 units. Always use another 30 to 60 pen to complete your dose and no other pen.

How to read the dose window

- **Do not** use the pen if your single daily dose is less than 30 units, shown as white numbers on a black background.



Units of medication in your pen

- Your pen contains a total of 300 units. You can select your dose in steps of 1 unit.
- **Do not** use this pen if you need a single daily dose that is less than 30 units, or more than 60 units.
- Each pen contains more than 1 dose.

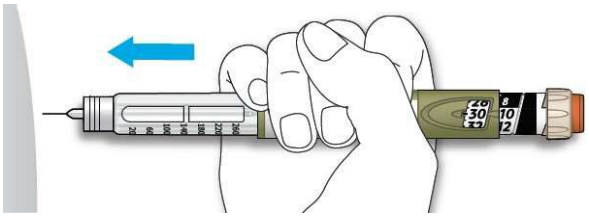
STEP 5: Inject the dose

- If you find it hard to press the injection button in, **do not** force it as this may break your pen. Seesection at the end of Step 5 for help.

5A: Choose a place to inject as shown in the picture above.

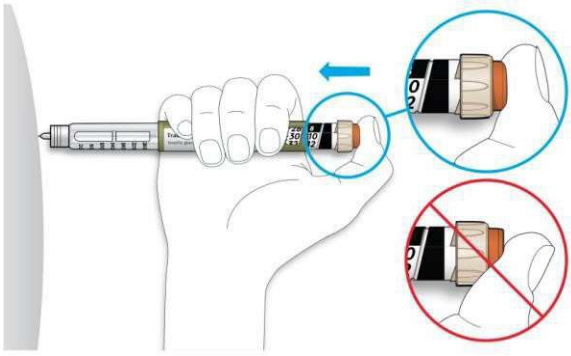
Step 5B: Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



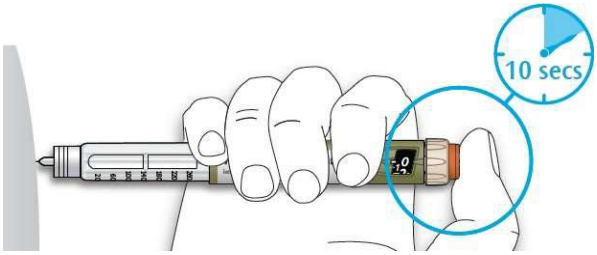
Step 5C: Place your thumb on the injection button. Then press all the way in and hold.

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



Step 5D: Keep the injection button held in and when you see "0" in the dose window, slowly count to10.

- This will make sure you get your full dose.



5E. After holding and slowly counting to 10, release the injection button. Then remove the needlefrom your skin.

If you find it hard to press the injection button in:

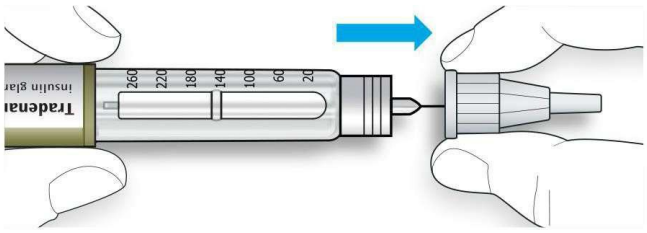
- Change the needle (**see STEP 6 and STEP 2**) then do a safety test (**see STEP 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove medication from your pen.

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.

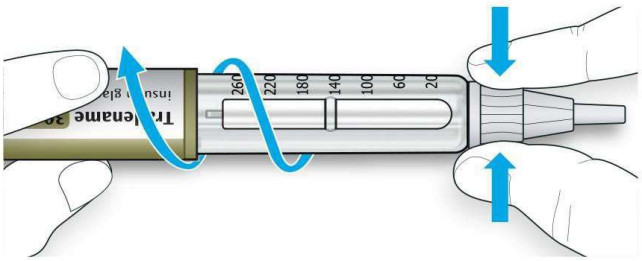
Step 6A: Grip the widest part of the outer needle cap. Keep the needle straight and guide it into theouter needle cap back. Then push firmly on.

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

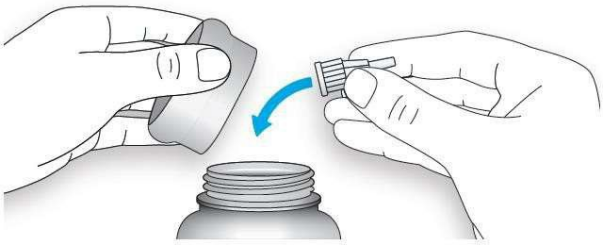


Step 6B: Grip and squeeze the widest part of the outer needle cap. Turn your pen several times withyour other hand to remove the needle.

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

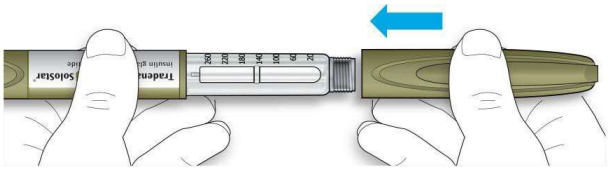


Step 6C: Throw away the used needle in a puncture resistant container (see "**Throwing your penaway**" at the end of this Instructions for Use).



Step 6D Put your pen cap back on.

- Do not put the pen back in the refrigerator.



Use by

- Only use your pen for up to **28 days** after its first use.

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** for 28 days
- **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.

How to care for your pen Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- 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 told by your pharmacist or local authority.

Manufactured by: M/s Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

Importer: Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, Vadape. Tal: Bhiwandi - 16(Thane Z5) Pin :421302

Marketed by: Sanofi India Ltd., CTS NO. 117-B, L&T Business park, Saki Vihar road, Powai. Mumbai- 400072.

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