PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSOLIQUA™

Insulin glargine and Lixisenatide injection

100 units/mL + 33 mcg/mL
Solution for injection in a prefilled pen for subcutaneous injection

Antidiabetic Agent

ATC Code: A10AE54

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RECENT MAJOR LABEL CHANGES

Not applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SOLIQUA, a fixed ratio combination of insulin glargine and lixisenatide, once daily injection, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.

Use alternative antidiabetic products if patients require basal insulin below 15 units or over 60 units (see DOSAGE AND ADMINISTRATION).

Patients on basal insulin or lixisenatide should not continue these drugs when beginning treatment with SOLIQUA, since SOLIQUA contains both basal insulin and a GLP-1 receptor agonist.

Limitations of Use

- SOLIQUA has not been studied with short acting insulin.
- SOLIQUA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- SOLIQUA is not recommended for use in combination with any other product containing lixisenatide or another GLP-1 receptor agonist.
- SOLIQUA has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas)
- SOLIQUA is not recommended for use in patients with gastroparesis

1.1 Pediatrics (<18 years of age)

The safety and efficacy of SOLIQUA in pediatric patients (<18 years of age) have not been established. Therefore, Health Canada has not authorized an indication for pediatric use. .

1.2 Geriatrics (> 65 years of age)

The therapeutic experience in patients ≥75 years of age is limited. SOLIQUA should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS – Special Populations)The dose should be adjusted on an individual basis, based on glucose monitoring (see DOSAGE AND ADMINISTRATION, Special Populations, Geriatrics).

2 CONTRAINDICATIONS

- SOLIQUA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (For a complete listing of ingredients, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).
- Pregnant or breastfeeding women.
- During episodes of hypoglycemia (see OVERDOSAGE).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

SOLIQUA contains insulin glargine. The following warnings pertain to the use of insulin.

- Hypoglycemia is the most common adverse effect of insulin products, including SOLIQUA (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). As with all insulin products, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes mellitus treated with insulins.

- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.

- Any change of insulin should be made cautiously and only under medical supervision.

- SOLIQUA is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

- SOLIQUA must not be mixed with any other insulin or diluted with any other solution. If SOLIQUA is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/ pharmacodynamic profile (e.g., onset of action, time to peak effect) of SOLIQUA and/or the other mixed product may be altered in an unpredictable manner (see DOSAGE AND ADMINISTRATION, SPECIAL HANDLING INSTRUCTIONS)

- SOLIQUA shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the cartridge (see SPECIAL HANDLING INSTRUCTIONS)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

SOLIQUA is titratable and available in a SoloSTAR pen:

- 1 unit of SOLIQUA contains 1 unit of insulin glargine and 0.33 mcg lixisenatide
- allows daily doses between 15 and 60 units of SOLIQUA (15 to 60 units insulin glargine/ 5 to 20 mcg lixisenatide).

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 the first meal. If a dose of SOLIQUA is missed, it should be injected within the hour prior to the next meal. An extra dose should not be taken to make up for the missed dose.

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.

Patients adjusting the amount or timing of dosing with SOLIQUA should only do so under medical guidance with appropriate glucose monitoring (see WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

Initiation of SOLIQUA:

Starting Dose of SOLIQUA:
Therapy with basal insulin should be discontinued prior to initiation of SOLIQUA.
The starting dose of SOLIQUA is selected based on prior basal insulin dose in the previous treatment and in order not to exceed the recommended lixisenatide starting dose of 10 mcg:

- In patients inadequately controlled on less than 30 units of basal insulin, the recommended starting dosage of SOLIQUA is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
- In patients inadequately controlled on 30 to 60 units of basal insulin, the recommended starting dosage of SOLIQUA is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily.

Starting dose of SOLIQUA

	Previous treatment	
	Basal insulin < 30 units	Basal insulin ≥ 30 units to < 60 units
SOLIQUA starting dose	15 Units (15 Units/5 mcg)*	30 Units (30 Units/10 mcg)*

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

4.3 Dosage titration of SOLIQUA

After starting with the recommended dosage of SOLIQUA, based upon prior insulin dose, the dosage is titrated upwards or downwards; by two to four units every week, based on self-monitored fasting plasma glucose results, patient's metabolic needs and until the target fasting plasma glucose is achieved (see CLINICAL TRIALS).

To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS)

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

Use alternative antidiabetic products if patients require SOLIQUA daily dosage:
- below 15 units, or
- over 60 units

Table 1 - Units of Insulin Glargine and Micrograms of Lixisenatide in Each Dosage of SOLIQUA

SOLIQUA (dose window display)*	Insulin glargine component dose	Lixisenatide component dose	Comment
2	---	---	Safety test dose – not for injection
15	15 units	5 mcg	Recommended starting dosage for patients previously treated with less than 30 units of basal insulin
16	16 units	5.3 mcg	
17	17 units	5.7 mcg	
18	18 units	6 mcg	
19	19 units	6.3 mcg	
20	20 units	6.7 mcg	
21	21 units	7 mcg	
22	22 units	7.3 mcg	
23	23 units	7.7 mcg	
24	24 units	8 mcg	
25	25 units	8.3 mcg	
26	26 units	8.7 mcg	
27	27 units	9 mcg	
28	28 units	9.3 mcg	
29	29 units	9.7 mcg	
30	30 units	10 mcg	Recommended starting dosage for patients previously treated with 30 to 60 units of basal insulin
31	31 units	10.3 mcg	
32	32 units	10.7 mcg	
33	33 units	11 mcg	
34	34 units	11.3 mcg	
35	35 units	11.7 mcg	
36	36 units	12 mcg	
37	37 units	12.3 mcg	

SOLIQUA (dose window display)*	Insulin glargine component dose	Lixisenatide component dose	Comment
38	38 units	12.7 mcg	
39	39 units	13 mcg	
40	40 units	13.3 mcg	
41	41 units	13.7 mcg	
42	42 units	14 mcg	
43	43 units	14.3 mcg	
44	44 units	14.7 mcg	
45	45 units	15 mcg	
46	46 units	15.3 mcg	
47	47 units	15.7 mcg	
48	48 units	16 mcg	
49	49 units	16.3 mcg	
50	50 units	16.7 mcg	
51	51 units	17 mcg	
52	52 units	17.3 mcg	
53	53 units	17.7 mcg	
54	54 units	18 mcg	
55	55 units	18.3 mcg	
56	56 units	18.7 mcg	
57	57 units	19 mcg	
58	58 units	19.3 mcg	
59	59 units	19.7 mcg	
60	60 units	20 mcg	Maximum daily dosage

Special Populations

Pediatrics (< 18 years of age)
The safety and effectiveness of SOLIQUA in pediatric patients below the age of 18 years have not been established. Health Canada has not authorized an indication for pediatric use.

Geriatrics *(≥65 years old)*
The therapeutic experience in patients ≥75 years of age is limited. SOLIQUA should be used with caution in patients 65 years and older (see WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics). In elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. Hypoglycemia may be difficult to recognize in the elderly (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). Careful glucose monitoring and dose adjustments of SOLIQUA on an individual basis are necessary in elderly patients. The initial dosing with SOLIQUA, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

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 (see WARNINGS AND PRECAUTIONS*).*

Renal impairment
No dosage adjustment is necessary for patients with mild (creatinine clearance: 60-90 mL/min) and moderate (creatinine clearance: 30-60 mL/min) renal impairment.

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. Close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended in these patients. Therapeutic experience with lixisenatide in patients with severe renal impairment is very limited, and there is no experience in patients with end stage renal disease or on dialysis. Therefore, use in these patients is not recommended.

4.4 Administration

Patients and caregivers should receive proper training prior to first use of SOLIQUA (see STORAGE, STABILITY AND DISPOSAL and SPECIAL HANDLING INSTRUCTIONS).
Administration is a subcutaneous injection either 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 (see ADVERSE REACTIONS).

To avoid dosing errors and potential for overdose, neither the patient nor healthcare professionals should use a syringe to draw the medicinal product from the cartridge in the pre-filled pen into a syringe.

4.5 Missed Dose

If a dose of SOLIQUA is missed, it should be injected within the hour prior to the next meal. Do not administer an extra dose or increase the dose to make up for the missed dose.

5 OVERDOSAGE

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.

Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Nocturnal hypoglycemia is common in people taking insulin and symptoms can include restlessness, making unusual noises, attempting to get out of bed or accidentally rolling out of bed, sleepwalking, nightmares and sweating. Patients may wake up with a headache in the morning if their blood sugar was low during the night.

Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal. In some cases, the first sign of hypoglycemia may be confusion or loss of consciousness (hypoglycemia unawareness). Severe hypoglycemia, resulting in seizures, is more likely to occur at nighttime (nocturnal hypoglycemia) than during the day.

Lixisenatide
During clinical trials, short term exposure of patients to lixisenatide at doses of up to 30 mg twice a day resulted in an increased incidence of gastrointestinal adverse reactions.

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. It is therefore recommended that patients with diabetes carry sugar-containing products.

More severe episodes culminating in coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon (1 mg for adult) by a trained person or concentrated intravenous glucose by a medical professional. 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.

Lixisenatide
In case of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and should include close monitoring of plasma glucose, hydration status and renal function. If SOLIQUA is to be continued, the SOLIQUA dose should be reduced to the prescribed dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution for injection in a prefilled pen: - 100 units insulin glargine + 33 mcg lixisenatide per mL	Glycerol, methionine, metacresol (2.7 mg/mL), zinc chloride, hydrochloric acid/ sodium hydroxide (for pH adjustment), water for injection.

Dosage form:
SOLIQUA is available as a sterile solution for injection in prefilled SoloSTAR pen:

- Each mL of solution contains 100 units insulin glargine and 33 mcg lixisenatide
- One pre-filled pen contains 3 mL equivalent to 300 units insulin glargine and 100 mcg lixisenatide.
- One unit of SOLIQUA contains 1 unit of insulin glargine and 0.33 mcg of lixisenatide.

The product is administered by subcutaneous injection.

Composition:
Active ingredient: Insulin glargine and lixisenatide

Excipients: Glycerol, methionine, metacresol (2.7 mg/mL), zinc chloride, hydrochloric acid/ sodium hydroxide (for pH adjustment), water for injection.

Packaging:
SOLIQUA is supplied in a disposable SoloSTAR pen, olive colored, containing a sterile solution for subcutaneous administration. Each prefilled pen contains 3 mL solution.

7 DESCRIPTION

SOLIQUA
SOLIQUA is a fixed ratio combination of insulin glargine and lixisenatide.

Insulin glargine
Insulin glargine (rDNA origin) is a recombinant human insulin analogue that is a long-acting, parenteral blood-glucose-lowering agent. It is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12 strain) as the production organism.

Insulin glargine differs from natural human insulin in that the amino acid asparagine at position 21 of the A-chain is replaced by glycine and two arginines are added to the C-terminus of the B-chain (see PHARMACEUTICAL INFORMATION).

Lixisenatide
Lixisenatide is a human glucagon-like peptide-1 receptor (GLP-1R) agonist for the treatment of type 2 diabetes mellitus. The structure of lixisenatide was based on exendin-4 (1-39), which was modified by adding six lysine residues C-terminally. These modifications enable the product to withstand physiological degradation by dipeptidyl peptidase IV.

8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General
SOLIQUA must not be administered by intravenous or intramuscular injection. SOLIQUA pens should never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

To avoid medication errors between SOLIQUA and other injectable products, patients should be instructed to always check the pen label before each injection (see ADVERSE REACTIONS).

Insulin glargine
As with all insulin preparations, the time course of SOLIQUA action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulin therapies, particularly when given intravenously. However, SOLIQUA should not be given intravenously or intramuscularly, or via an insulin pump (see DOSAGE AND ADMINISTRATION). If left untreated, hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. This potential clinical adverse effect may be more relevant in patients who are at risk for hypokalemia (e.g., patient using potassium lowering drugs), patients taking medications sensitive to serum potassium concentrations, or patients losing potassium through other means (e.g. diarrhea).

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements.

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Patients with human insulin antibodies may be hypersensitive to other insulins, with a risk of hypoglycemia and/or cross-reactivity.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of TZD with insulin is not indicated for the treatment of Type 2 Diabetes Mellitus. SOLIQUA should not be used in combination with TZDs.

Carcinogenesis and Mutagenesis

Lixisenatide

Risk of thyroid C-cell tumours:
Lixisenatide administration to mice and rats for 2 years resulted in thyroid C-cell neoplasia. C-cell carcinomas were confined to rats at human systemic lixisenatide exposure ratios ≥35-fold, while increased incidences of C-cell hyperplasia and adenoma occurred at exposure ratios of >128-fold in mice and ≥9-fold in rats, with a no-effect level not identified in rats (see NON-CLINICAL TOXICOLOGY, Lixisenatide, Carcinogenesis).

Other GLP-1 receptor agonists have been shown to cause thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in rats and mice. The relevance of these results to humans has not yet been determined. Until further long-term data in humans are available, caution is advised when prescribing SOLIQUA in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Cardiovascular

Lixisenatide
Heart Rate Increase:
Lixisenatide causes an increase in heart rate in clinical trials in healthy subjects undergoing serial electrocardiogram (ECG) monitoring and in patients with type 2 diabetes mellitus undergoing 24 hour ambulatory heart rate monitoring. Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as tachyarrhythmias (see DRUG INTERACTIONS). .

PR Interval Prolongation:
Lixisenatide causes a prolongation of the PR interval of the ECG (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Caution should be observed in patients with pre-existing conduction system abnormalities (e.g. marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g. tachyarrhythmias).

Physicians should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug (see DRUG INTERACTIONS).

Driving and Operating Machinery

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 or operating a vehicle or potentially dangerous 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.

Endocrine and Metabolism

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. Early warning symptoms of hypoglycemia may be different, be less pronounced or absent under certain conditions, as for example, in patients whose glycemic control is markedly improved, in elderly patients, in patients where an autonomic neuropathy is present, in patients whose hypoglycemia is developing gradually, in patients with a long history of diabetes, in patients with psychiatric illness, or in patients receiving concurrent treatment with certain other drugs such as beta-blockers.

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, diarrhea)
- 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 DRUG INTERACTIONS).

Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of administration is changed.

As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma or death (see ADVERSE REACTIONS).

As with all insulins, additional caution (including intensified blood glucose monitoring) should be exercised in patient populations who are at greater risk for clinically significant sequelae from hypoglycemic episodes.

The dose of SOLIQUA must be individualized based on clinical response and is titrated based on the patient's need for insulin (see DOSAGE AND ADMINISTRATION).

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

Hypoglycemic reactions following treatment with insulin products such as SOLIQUA are mostly mild and easily managed. Changes in insulin therapy or changes in life style (i.e. diet, omission of a meal, exercise/ physical activity) may require a change in dosage to avoid hypoglycemia. Glucose monitoring is recommended for all patients with diabetes.

Diabetic patients should be instructed to carry a few lumps of sugar, candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur (see PATIENT MEDICATION INFORMATION).

Hyperglycemia:
The use of too low insulin dosages or discontinuation of treatment, may lead to hyperglycemia and diabetic ketoacidosis. Uncorrected hyperglycemic reactions can cause loss of consciousness, coma, or death.

Gastrointestinal

Lixisenatide
Patients with Severe Gastrointestinal Disease:
Use of glucagon-like peptide-1 (GLP-1) receptor agonists, including lixisenatide, is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhea. Lixisenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis, a history of stomach/gastric surgery, or inflammatory bowel disease, and therefore, the use of SOLIQUA is not recommended in these patients.

Lixisenatide slows gastric emptying, and thereby reduces the rate of absorption of orally administered drugs (see DRUG INTERACTIONS).

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 DRUG 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.

Hepatic/Biliary/Pancreas

Lixisenatide
Pancreatitis:
Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported in patients treated with GLP-1 receptor agonists, and cases of pancreatitis have occurred in patients treated with lixisenatide during clinical trials. Patients should be informed of the characteristic symptoms of acute pancreatitis, such as persistent, severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting. If pancreatitis is suspected, SOLIQUA should be discontinued and appropriate management initiated promptly. If pancreatitis is confirmed, SOLIQUA should not be restarted. Consider other antidiabetic therapies in patients with a history of pancreatitis or in patients with other risk factors for pancreatitis (e.g. gallstones, alcoholism, or hypertriglyceridemia).

Immune

Anaphylaxis and Serious Hypersensitivity Reactions:
SOLIQUA is contraindicated in patients with known hypersensitivity to this drug or its contents (see CONTRAINDICATIONS).

If a hypersensitivity reaction is suspected, the patient should discontinue SOLIQUA and seek immediate medical attention.

In lixisenatide clinical trials, there have been cases of anaphylaxis determined to be related to lixisenatide. Other serious hypersensitivity reactions, including angioedema also occurred.

Patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist should be informed of and carefully monitored for allergic reactions, since it is unknown whether such patients will be predisposed to anaphylaxis with SOLIQUA.

Immunogenicity:
Administration of SOLIQUA may cause formation of antibodies against insulin glargine and/or lixisenatide. A pooled analysis of studies of lixisenatide-treated patients showed that 70% were antibody positive at Week 24 (see ADVERSE REACTIONS). A higher incidence of allergic reactions and injection site reactions occurred in antibody positive patients. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed.

If a patient receiving SOLIQUA displays worsening glycemic control or failure to achieve targeted glycemic control, or if significant injection site reactions or allergic reactions occur, alternative antidiabetic therapy should be considered.

Injection Site and Local Allergic Reactions:
As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching at the injection site, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients.

Rarely, SC administration of insulin products can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions.

Renal

Renal impairment
There is no therapeutic experience with SOLIQUA in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease. SOLIQUA is not recommended in patients with severe renal impairment or end-stage renal disease (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Special population, Renal).

Acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis or kidney transplantation, has been reported post-marketing in patients treated with GLP-1 receptor agonists (see ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions). Some of these events were reported in patients without known underlying renal disease. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration.

Since treatment with SOLIQUA may induce nausea, vomiting and diarrhoea with transient hypovolemia, which may worsen renal function, monitor renal function when initiating or escalating doses of SOLIQUA in patients with renal impairment and in patients reporting severe gastrointestinal reactions (see Monitoring and Laboratory Tests). Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Retinopathy

A marked change in glycemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, as for all insulin regimens, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycemic episodes may result in transient amaurosis.

Monitoring and Laboratory Tests

Anticoagulation:
International normalized ratio (INR) should be monitored frequently when initiating or discontinuing SOLIQUA when co-administered with warfarin (see DRUG INTERACTIONS).

Renal Function:
Assessment of renal function is recommended prior to initiation of SOLIQUA and periodically thereafter, as appropriate (see WARNINGS AND PRECAUTIONS, Renal).

Blood Glucose Monitoring
Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In elderly patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring and dose adjustments of SOLIQUA as necessary are recommended.

8.1 Special Populations

8.1.1 Pregnant Women

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 (see CONTRAINDICATIONS).

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

Insulin glargine
Post Marketing data on pregnant women (more than 1000 pregnancy outcomes) with insulin glargine indicate no specific adverse effects of insulin glargine on maternal and fetal/neonatal outcomes. Animal data do not indicate reproductive toxicity with insulin glargine.

Lixisenatide
Studies in animals have shown reproductive toxicity.

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

8.1.2 Breast-feeding

SOLIQUA should not be used during breast-feeding (see CONTRAINDICATIONS), there are no clinical data in nursing women. It is unknown if SOLIQUA is excreted in human milk. Lixisenatide was excreted in rat milk.

8.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available in pediatric patients (<18 years of age); therefore, Health Canada has not authorized an indication for pediatric use.

8.1.4 Geriatrics

The therapeutic experience in patients ≥75 years of age is limited. SOLIQUA should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, Special Populations-Geriatrics). The dose should be adjusted on an individual basis, based on glucose monitoring. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Hypoglycemia may be difficult to recognize in the elderly. In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements. Careful glucose monitoring and dose adjustments of SOLIQUA may be necessary.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

Summary of the safety profile
The SOLIQUA phase 3 clinical studies included 834 patients treated with SOLIQUA.
The most frequently reported undesirable adverse reactions during treatment with SOLIQUA were hypoglycemia and gastrointestinal adverse reactions (see Table 3 and Table 4).

The incidence of treatment discontinuation due to treatment-emergent adverse events was 2.6% for SOLIQUA compared to and 1.4% in the insulin glargine arm during the main treatment period of the 2 pooled placebo-controlled efficacy/safety studies. The most common treatment-emergent adverse events which led to treatment discontinuation in the SOLIQUA group were nausea (0.7%) and urticaria (0.4%).

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of SOLIQUA has been evaluated in two clinical studies (30 weeks duration) in type 2 diabetes patients (n=834) with a mean treatment duration of 203 days. The studies had the following characteristics: mean age was approximately 59 years; approximately 50% were male, 90% were Caucasian, 6% were Black or African American and 18 % were Hispanic. The mean duration of diabetes was 10.3 years; mean HbA1c at screening was 8.32. The mean BMI at baseline was 32 kg/m^2. Baseline eGFR was ≥60 mL/min in 87.2% of the pooled study population and mean baseline eGFR was 83.0 ml/min/1.73m².

Table 3: Adverse reactions reported in ≥ 2% of SOLIQUA-treated patients and occurring more frequently compared to either insulin glargine or lixisenatide groups

Adverse Reaction	SOLIQUA* (insulin glargine / lixisenatide) (n=834)	Insulin glargine* (n=832)	Lixisenatide** (n=233)
GASTROINTESTINAL DISORDERS			
Nausea	83 (10.0%)	19 (2.3%)	56 (24.0%)
Diarrhea	58 (7.0%)	30 (3.6%)	21 (9.0%)
Vomiting	28 (3.4%)	9 (1.1%)	15 (6.4%)
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	58 (7.0%)	57 (6.9%)	15 (6.4%)
Upper respiratory tract infection	46 (5.5%)	34 (4.1%)	12 (5.2%)
Influenza	30 (3.6%)	22 (2.6%)	4 (1.7%)
Urinary tract infection	19 (2.3%)	12 (1.4%)	4 (1.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Back pain	22 (2.6%)	15 (1.8%)	8 (3.4%)
NERVOUS SYSTEM DISORDERS			
Headache	45 (5.4%)	25 (3.0%)	18 (7.7%)
Dizziness	24 (2.9%)	12 (1.4%)	7 (3.0%)

* Pool of studies: ECF12404 and EFC12405
** EFC12404

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, and insulin containing products including SOLIQUA (see WARNINGS AND PRECAUTIONS, Endocrine, Metabolism).

Table 4 - Documented symptomatic or severe hypoglycemic adverse reactions

	Documented symptomatic hypoglycemia*		Severe hypoglycemia**
	Patients with event, n (%)	Events per patient-year, n	Events per patient-year, n
Pooled Phase 3 controlled studies			
Soliqua (n=834)	266 (31.9%)	2.13	0.01
Insulin glargine (n=832)	265 (31.9%)	2.55	<0.01
Lixisenatide (N=233)	15 (6.4%)	0.34	0
EFC12405			
Soliqua (n=365)	146 (40.0%)	3.03	0.02
Insulin glargine (n=365)	155 (42.5%)	4.22	<0.01
EFC12404			
Soliqua (n=469)	120 (25.6%)	1.44	0
Insulin glargine (n=467)	110 (23.6%)	1.22	<0.01
Lixisenatide (n=233)	15 (6.4%)	0.34	0

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

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.

Gastrointestinal disorders
Gastrointestinal adverse reactions (nausea, vomiting and diarrhea) were frequently reported adverse reactions during the treatment period. In pooled data from 2 phase 3 studies 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 lixisenatide (in study EFC12404), the incidence of related nausea, diarrhea and vomiting was 22.3%, 3% and 3.9%, respectively.

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. To reduce the risk of lipodystrophy, rotate the injection site between regions (abdomen,

thigh, or deltoid) or within regions, from one injection to the next (see WARNINGS AND PRECAUTIONS, Immune).

Immune system disorders
Allergic reactions (urticaria) possibly related with SOLIQUA has 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.

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

Peripheral Edema
Some patients taking insulin glargine, a component of SOLIQUA have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

9.3 Less Common Clinical Trial Adverse Reactions

The following is a list of less common treatment-emergent adverse events reported in the phase 3 clinical trials. Adverse events reported in <2% and reported in greater frequency in SOLIQUA-treated patients than in either insulin glargine- or lixisenatide-treated patients are included in the listing.

Gastrointestinal disorders: abdominal pain upper, dyspepsia.
Infections and infestations: acute sinusitis, acute tonsillitis, cystitis, gastroenteritis, infectious diarrhea, lower respiratory tract infections, pharyngitis, pharyngotonsilitis, rhinitis, sinusitis, tonsillitis, urethritis, viral gastroenteritis, viral infection, viral upper respiratory tract infection, viral sinusitis.
Nervous system Disorders: Head discomfort, post-traumatic headache
Musculoskeletal and connective tissue disorders: pain in extremity, neck pain.
General disorders and administration site conditions: asthenia, injection site discomfort, injection site irritation, injection site nodule, injection site bruising, injection site papule, injection site rash.

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Increases in serum calcitonin:

In the lixisenatide long-term cardiovascular outcomes trial, levels of serum calcitonin, a marker for thyroid C-cell proliferation, were elevated to ≥50 ng/L in 12 patients in the lixisenatide group (0.4%) and 2 patients in the placebo group (<0.1%). Similar elevations were seen a pool of Phase 2/3 studies, however reporting of calcitonin elevations in these trials was less consistently implemented. The clinical significance of these elevations is unclear.

9.5 Post-Market Adverse Drug Reactions

Renal:
In patients treated with GLP-1 receptor agonists, there have been post-marketing reports of acute renal failure and worsening of chronic kidney failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

Other:
Accidental mix-ups between insulin products have been reported. To avoid medication errors between SOLIQUA and other insulin products, instruct patients to always check the label before each injection.

10 DRUG INTERACTIONS

10.1 Overview

Interaction studies with SOLIQUA have not been performed.

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

Lixisenatide

When lixisenatide is co-administered with sulfonylurea or basal insulin, there is a potential risk of hypoglycemia. A reduction of the concomitantly administered sulfonylurea or basal insulin may be necessary based on clinical experience

Co-administration of lixisenatide with drugs that increase heart rate or prolong the PR interval should be undertaken with caution.

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 requires 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, or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered at least 1 hour before SOLIQUA injection.

Patients taking oral contraceptives should be advised to take them at least 1 hour before SOLIQUA administration or at least 11 hours after the dose 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, somatostatin analog (e.g. octreotide), sulfonamide antibiotics. Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA is coadministered with these drugs.

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). Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA is coadministered with these drugs.

Beta-blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Increased frequency of glucose monitoring and dose adjustment may be required when SOLIQUA is coadministered with these drugs.

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. Increased frequency of glucose monitoring may be required when SOLIQUA is coadministered with these drugs.

Other:
The use of TZDs in combination therapy with insulin is not indicated to avoid the risk of developing new or worsening heart failure (see WARNINGS AND PRECAUTIONS).

10.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 - Established or Potential Drug-Drug Interactions with lixisenatide

Co-administered drug	Lixisenatide	Ref	Effect	Clinical comment and alteration of dosing
Acetaminophen 1000 mg, single dose	10 µg, single dose	CT	No change in AUC_{last} and AUC_{inf} of acetaminophen whether administered before or after lixisenatide. C_{max} decreased by 29% and 31% and median t_{max} was delayed by approximately 2 and 1.75 hours if acetaminophen was administered 1 or 4 hours after lixisenatide.	No dose adjustment of acetaminophen is required when co-administered with SOLIQUA. Recommended to take acetaminophen 1 hour before SOLIQUA injection.
Oral contraceptive 0.03 mg EE and 0.15 mg levonorgestrel, single dose	10 µg, single dose	CT	Administration of oral contraceptives (ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after subcutaneous injection of lixisenatide 10 µg, did not change the C_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$ and t_{max} of ethinyl estradiol and levonorgestrel. No change in AUC_{last} and AUC_{inf}, $t_{1/2}$ of EE or levonorgestrel if oral contraceptive was administered 1-4 hours after lixisenatide. C_{max} of ethinyl estradiol and levonorgestrel decreased by 52% and 46% and t_{max} was delayed by 2 and 3 hours if oral contraceptive was administered 1 hour after lixisenatide. C_{max} of ethinyl estradiol and levonorgestrel decreased by 39% and 20% and t_{max} was delayed by 1 hour each if oral contraceptive was administered 4 hours after lixisenatide.	No dose adjustment of oral contraceptive is required when co-administered with SOLIQUA. It is recommended that oral contraceptives be administered at least 1 hour before or at least 11 hours after SOLIQUA administration.

Co-administered drug	Lixisenatide	Ref	Effect	Clinical comment and alteration of dosing
Atorvastatin 40 mg, repeated dosing	20 µg, repeated dosing	CT	Co-administration with atorvastatin in the morning had no effect on AUC_{0-24h} whereas C_{max} decreased by 31% and median t_{max} was delayed by 3.25 hours. If atorvastatin was administered in the evening, no such effect on t_{max} was observed while AUC_{0-24h} and C_{max} were increased by 27% and 66%, respectively.	No dose adjustment of atorvastatin is required when co-administered with SOLIQUA. Recommended to take atorvastatin 1 hour before SOLIQUA injection.
Warfarin 25 mg, repeated dosing	20 µg, repeated dosing	CT	No effects on S-warfarin AUC_{last} and AUC_{inf} or INR (International Normalized Ratio) while C_{max} was reduced by 19% and t_{max} was delayed by 7 hours.	No dose adjustment of warfarin is required when co-administered with SOLIQUA, but frequent INR monitoring is recommended at start or end of SOLIQUA treatment (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests).
Digoxin 0.25 mg, repeated dosing	20 µg, repeated dosing	CT	No change in AUC_{0-24h} of digoxin whereas C_{max} was reduced by 26% and t_{max} of digoxin was delayed by 1.5 hours.	No dose adjustment of digoxin is required when co-administered with SOLIQUA.
Ramipril 5 mg, repeated dosing	20 µg, repeated dosing	CT	Increase in the AUC_{0-24h} of ramipril by 21% while the C_{max} was decreased by 63%. The AUC_{0-24h} and Cmax of the active metabolite (ramiprilat) were not affected. T_{max} of ramipril and ramiprilat was delayed by 2.3 hours for Ramipril and 3 hours for Ramiprilat.	No dose adjustment of ramipril is required when co-administered with SOLIQUA.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drugs that Increase Heart Rate:
Lixisenatide causes an increase in heart rate. The impact on heart rate of co-administration of lixisenatide with other drugs that increase heart rate (e.g. sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of SOLIQUA with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation:
Lixisenatide causes an increase in the PR interval. The impact on the PR interval of co-administration of lixisenatide with other drugs that prolong the PR interval (including, but not

limited to, antiarrhythmics, calcium channel blockers, beta-adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of SOLIQUA with these drugs should be undertaken with caution.

10.3 Drug-Food Interactions

Interactions with food have not been established.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10.6 Drug-Lifestyle Interactions

No studies on the effects on the ability to drive and use machines have been performed.

The patient's ability to concentrate and react may be impaired as a result of 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. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

SOLIQUA is a combination of insulin glargine, a basal insulin analog, and lixisenatide, a GLP-1 receptor agonist.

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

Lixisenatide
Lixisenatide is a GLP-1 receptor agonist. Lixisenatide increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.

11.2 Pharmacodynamics

Insulin glargine
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.

Lixisenatide
In a clinical pharmacology study in adults with type 2 diabetes mellitus, 20 µg once daily administration of lixisenatide given before the first meal, reduced fasting plasma glucose level and postprandial blood glucose $AUC_{0\text{-}300min}$ compared to placebo (-1.88 mmol/L and -21.5 h·mmol/L, respectively) following a standardized test meal. The effect on postprandial blood glucose AUC was most notable with the first meal, and the effect was attenuated with later meals in the day.

Glucagon secretion:
Treatment with lixisenatide 20 µg once daily reduced postprandial glucagon levels ($AUC_{0\text{-}300min}$) compared to placebo by -15.6 h·pmol/L after a standardized test meal in patients with type 2 diabetes.

Insulin secretion:
Lixisenatide restores the first-phase insulin response in patients with type 2 diabetes in a glucose-dependent manner by 6.6-fold (90% CI: 5.0, 8.7) and increases the second-phase insulin response by 3.0-fold (90% CI: 2.7, 3.3) compared with placebo as measured by AUC.

Gastric emptying:
Following a standardized labelled test meal, lixisenatide slows gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation. The delay of gastric emptying with lixisenatide was maintained in an 8-week study in patients with type 2 diabetes mellitus.

Gallbladder Motility:
In a randomised, double-blind, placebo-controlled, crossover study, gallbladder motility was assessed in 24 healthy subjects who received single subcutaneous injections of 20 µg lixisenatide and placebo. Lixisenatide treatment caused statistically significant reductions in gall bladder ejection fraction (GBEF) in response to cholecystokinin-8, with mean differences from placebo in GBEF of 41.4% (95% CI: 28.6, 54.2) at 30 minutes and 45.8% (95% CI: 29.9, 61.7) at 60 minutes.

Cardiac electrophysiology:
A randomised, double-blind, double-dummy, repeated-dose, placebo-controlled, parallel group ECG assessment study was performed to assess the effect of lixisenatide at subcutaneous doses of 20 µg once daily and a supratherapeutic dose of 30 µg twice daily for 28 days in healthy subjects (N=60-62/treatment group). ECG assessments were performed at baseline and on day 28 of treatment.

Heart Rate: Lixisenatide was associated with increases in heart rate. In the lixisenatide 20 µg once daily group, the maximum difference from placebo in mean change from baseline heart rate was 7.3 bpm (90% CI: 5.6, 9.0) at the 4 h time point. In the lixisenatide 30 µg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline heart rate was 8.6 bpm (90% CI: 7.0, 10.3) at 4 h. The 24 h time-averaged increase in mean heart rate was 3.9 (20 µg once daily group), 5.8 bpm (30 µg twice daily group), and 2.6

bpm (placebo).

PR Interval: Lixisenatide resulted in PR interval prolongation. In the lixisenatide 20 µg once daily group, the maximum difference from placebo in the mean change from baseline PR interval was 3.7 ms (90% CI: 0.6, 6.7) at the 1 h time point. In the lixisenatide 30 µg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline PR interval was 5.0 ms (90% CI: 2.0, 8.0) at 1 h.

QTcF Interval: In the lixisenatide 20 µg once daily group, the maximum difference from placebo in the mean change from baseline in QTcF interval (QTcF = $QT/RR^{0.33}$) was 4.6 ms (90% CI: 2.3, 6.9) at the 3 h time point. In the lixisenatide 30 µg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline QTcF was 5.5 ms (90% CI: 3.2, 7.8) at 3 h. Caution should be observed in patients with risk factors for torsade de pointes (e.g. congenital long QT syndrome, cardiac disease, electrolyte abnormalities).

Ambulatory Heart Rate Monitoring: In an open-label, randomised, active-controlled, parallel group study of lixisenatide in patients with type 2 diabetes not adequately controlled with insulin glargine, with or without metformin, lixisenatide 20 µg was administered for 8 weeks (N=46). Ambulatory heart rate monitoring performed on day 57/58 showed a mean change from baseline in daytime mean heart rate of 3.67 bpm (95% CI: 0.86, 6.48) and a mean change from baseline in nighttime mean heart rate of 2.20 bpm (95% CI: -0.72, 5.11).

11.3 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:

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 (100 units/mL) 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.

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Distribution:

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

Metabolism and Elimination:

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 is assumed to be eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation.

After multiple dose 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 and Conditions

Age, Race, 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, gender, and race do not have a clinically meaningful effect on pharmacokinetics of lixisenatide.

Pediatrics: SOLIQUA should not be used in pediatric patients. The safety and effectiveness of SOLIQUA in patients below the age of 18 years have not been established.

Geriatrics: SOLIQUA should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals to lixisenatide cannot be ruled out.

Hepatic Insufficiency:
No pharmacokinetic studies were performed for lixisenatide or insulin glargine in patients with hepatic insufficiency.

Renal Insufficiency:
Compared to healthy subjects (N=4; CLcr greater than or equal to 90 mL/min), plasma Cmax of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild (N=9), moderate (N=11), and severe (N=8) renal impairment (CLcr 60-89, 30-59 and 15-29 mL/min), respectively; plasma AUC_{inf} was increased by approximately 46%, 51% and 87% with mild, moderate and severe renal impairment, respectively.

Insulin glargine
No pharmacokinetic studies were performed in patients with renal insufficiency.

Body weight:
Effect of Body Mass Index (BMI) on the pharmacokinetics of SOLIQUA has not been evaluated.

Lixisenatide
The population pharmacokinetic analysis showed that lixisenatide exposure decreased with increasing body weight in a nonlinear manner, with greater changes for low body weights.

12 STORAGE, STABILITY AND DISPOSAL

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 up to 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.

Discard the pen 28 days after first use, or if exposed to excessive heat or freezing.

13 SPECIAL HANDLING INSTRUCTIONS

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.

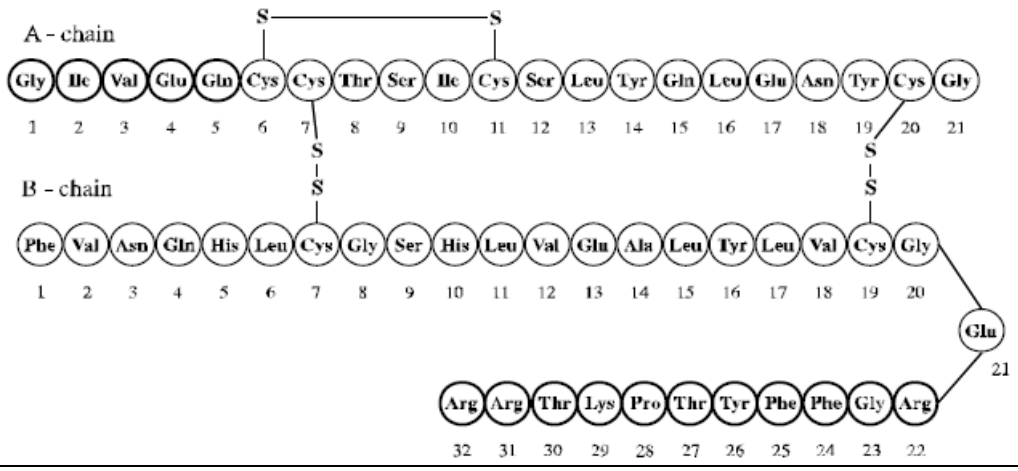
The label must always be checked before each injection to avoid medication errors between SOLIQUA and other injectable antidiabetic medicinal products.

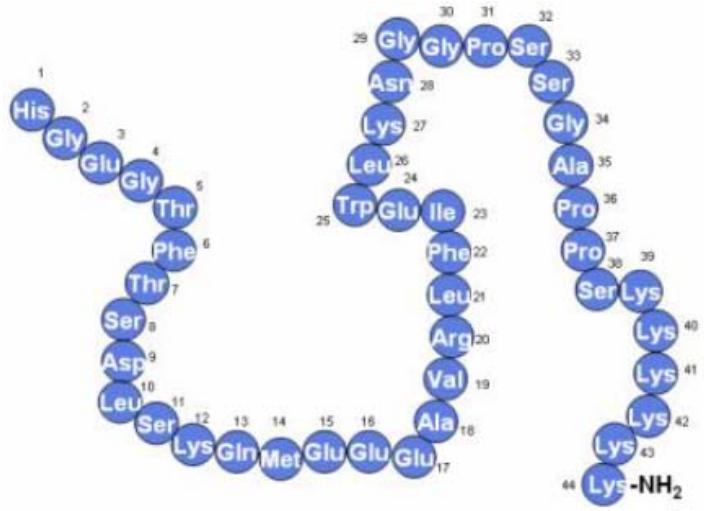
Before using SOLIQUA, the instructions for use included in the package leaflet must be read carefully.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Insulin glargine Recombinant human insulin analogue	lixisenatide
Chemical name:	21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin	H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys-NH2
Molecular formula and molecular mass:	$C_{267}H_{404}N_{72}O_{78}S_6$ 6063 Daltons	$C_{215}H_{347}N_{61}O_{65}S$ 4858.5
Physicochemical properties:	fine white powder	Amorphous, hygroscopic, white to off-white powder.
Solubility at 25°C	3 to 7 mcg/mL at pH 7 at least 10 mg/mL at pH 5, greater than 100 mg/mL at pH 2	Citrate buffer, pH from 2 to 10: ~6 mg/mL, at all pH values Phosphate buffer, pH from 2 to 9: ~6 mg/mL, at all pH
Structural formula:	Insulin glargine:  	

	Lixisenatide: 

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Table 6- Summary of patient demographics for clinical trials.

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender (M/F)
EFC 12404*	Open-label, randomized, 3-arm parallel group Active-controlled (insulin glargine and lixisenatide)	- SOLIQUA: initial dose of 10 U/5 mcg, to a maximum dose of 60 U/20 mcg, SC injection. - Insulin glargine: initial dose of 10 U to a maximum dose of 60 U, SC injection. - Lixisenatide: 10 mcg QD for 2 weeks, then a maintenance dose of 20 mcg QD SC injection SOLIQUA: SC injection using the SoloSTAR® disposable pen-injector device 30 weeks	1170	58.4 (18-82)	592/578

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender (M/F)
EFC 12405	Open-label, randomized, 2-arm parallel group Active-controlled (insulin glargine)	*SOLIQUA Starting dose::* 20 U/10 mcg (SC injection) if glargine dose on the day before randomization was <30 U; 30U/10 mcg (SC injection) if glargine dose on the day before randomization was ≥30 U. The dose was to remain stable for 2 weeks. *Insulin glargine Starting dose:* Same dose as that received on the day before randomization. *SOLIQUA* and Insulin glargine were adjusted once weekly Maximum FRC dose: 60 U/20 mcg The maximum daily insulin glargine dose: 60 U. SOLIQUA: SC injection using the SoloSTAR® disposable pen-injector device 30 weeks	736	60.0 (32-85)	344/392

* Non-approved indication, Supportive study (safety and PK/PD).

Overview of Clinical Studies

The safety and effectiveness of SOLIQUA on glycemic control were evaluated in two active controlled, open label, randomized clinical studies in patients with type 2 diabetes mellitus:

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 7 below.

Table 7 - Dose adjustment algorithm SOLIQUA

Fasting self-measured plasma glucose (mmol/L)	Dose change (units/day)
>7.8	+4
>5.6 and ≤7.8	+2
4.4 to 5.6	No change
<4.4	-2

15.2 Study Results

Clinical Studies in Patients with Type 2 Diabetes Uncontrolled on Basal Insulin alone or in combination with metformin

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 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) and had an HbA1c between 7.5% and 10%.

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≤ 7.8 mmol/L and insulin glargine daily dose of 20 to 50 units, were randomized to either SOLIQUA (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 8 and Figure 1).

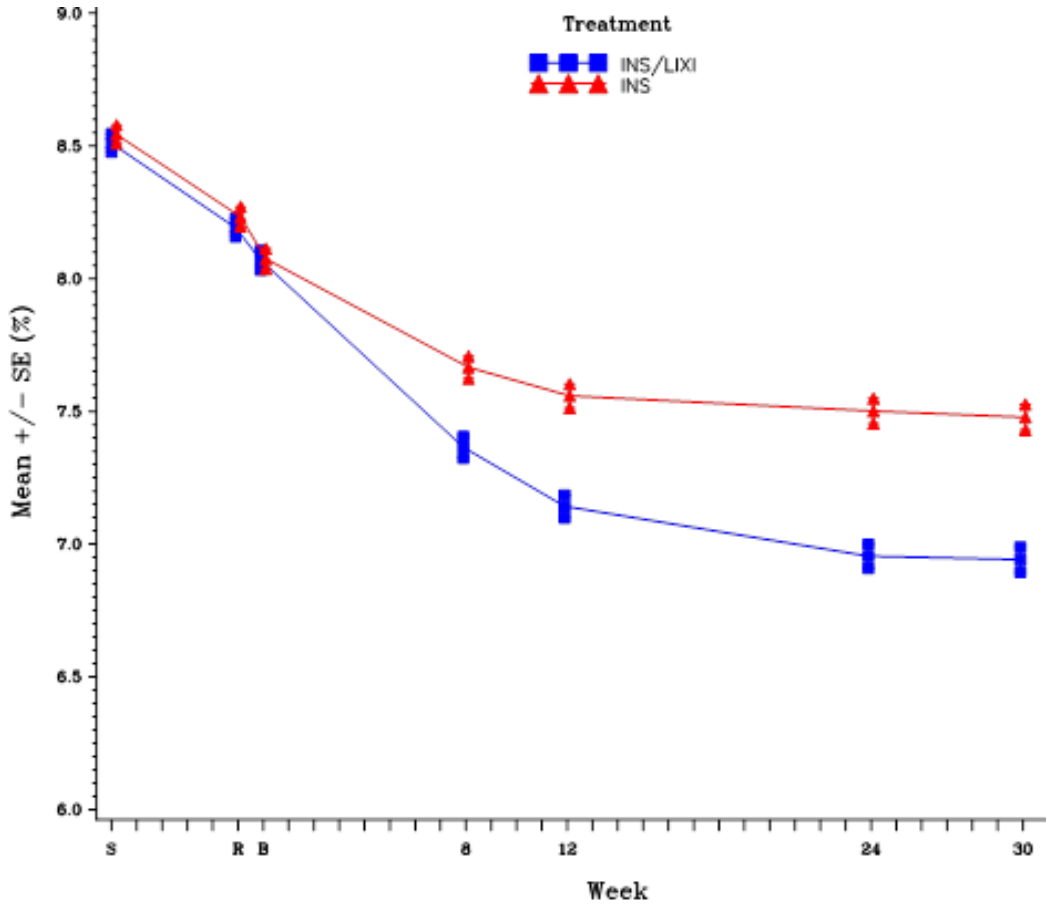
This trial was designed to show the contribution of the GLP-1 component to glycemic lowering. The insulin glargine dose in this trial was capped at a maximum dose of 60 units and the dosing algorithm was selected to isolate the effect of the GLP-1 component. At the end of the trial, the doses of insulin glargine were equivalent between treatment groups. The mean final dose of SOLIQUA and insulin glargine at week 30 was 46.7 units (for SOLIQUA: 46.7 units insulin glargine/15.6 mcg lixisenatide). The difference in effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where alternative insulin glargine dosage can be used.

Table 8 - 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%)
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)	

There was a statistical significant difference between the SOLIQUA-treated patients vs the insulin glargine-treated patients in the percentage of patients reaching HbA1C < 7% with no body weight gain at week 30 ($p < 0.0001$).

Figure 1- Mean HbA1c (%) at start of screening, at randomization, Each Time Point (Completers) and at Week 30 (LOCF*) - mITT population



*LOCF = Last observation carried forward.

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.

Lixisenatide

The 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. 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.

The incidence of the primary endpoint was similar in the lixisenatide and placebo groups: the hazard ratio (HR) for lixisenatide versus placebo was 1.02, with an associated 2-sided 95% confidence interval (CI) of 0.89 to 1.17. The upper bound of this confidence interval excluded a risk margin larger than 1.3, thus demonstrating non-inferiority to placebo. Superiority to placebo was not demonstrated. Hazard ratios for the other adjudicated endpoints were not statistically significant.

Insulin glargine

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 12,537 patients study that compared insulin glargine 100 Units/mL 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.

16 NON-CLINICAL TOXICOLOGY

SOLIQUA

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

Insulin glargine

Acute toxicity
The acute toxicity of i.v. and s.c. administration of insulin glargine was tested in mice and rats. The LD50 in each species was in the range of greater than or equal to 1000 U/kg.

Chronic toxicity:
In repeated subcutaneous dose toxicity studies of insulin glargine in mice, rats, and dogs only expected pharmacodynamic results were observed.

Carcinogenesis
The carcinogenic potential of insulin glargine was evaluated in mice and rats at three different dose levels. These two-year carcinogenicity studies were performed in mice and rats. The results do not suggest a cancer risk to humans.

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 U (0.008 mg/kg/day), based on mg/m^2 . The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. No clear explanation was found for the excessive mortalities. A similar effect was seen in the female mice control groups: the saline controls mortality (34%) was comparable to the mortality of high dosed female mice (28%) whereas in

the vehicle controls mortality reached 42% which is in the same range as the mortality of low dosed female mice (46%). In contrast, the mortality was the same in the male mice saline and vehicle control groups (both 16%). Therefore, these findings are considered as an accidental one due to biological variability. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Mutagenesis
Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

Impairment of fertility
In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 U (0.008 mg/kg/day), based on mg/m^2, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Embryo fetal development
In an embryotoxicity study in rats, hypoglycemia, but no maternal toxicity, occurred. Insulin glargine was not embryotoxic and not teratogenic. In an embryotoxicity study in rabbits, maternal (hypoglycemic shock, intrauterine deaths) and embryo-fetal hypoglycemia-induced toxicity, including single anomalies in the middle- and high-dose groups, were observed. Similar effects were observed with NPH human insulin.

Studies in rats with doses up to 40 times the average daily basal human dose (0.5 U/kg) and a study in rabbits at two times the human dose (0.5 U/kg) do not indicate direct harmful effects on the pregnancy during the different stages of pregnancy. The effects of insulin glargine did not generally differ from those observed with regular human insulin; however, in rabbits, five fetuses from 2 litters of the high dose group exhibited dilation of the cerebral ventricles.

Lixisenatide

Acute Toxicity
A single dose of 500, 5000, and 100 µg/kg iv or 500, 5000, and 200 µg/kg s.c. was tolerated without mortality in mice, rats, and dogs, respectively.

Repeat Dose Toxicity
The repeated dose toxicity of lixisenatide after s.c. twice daily (8 h apart) administration was evaluated in mice, rats, and dogs for up to 13, 26, and 52 weeks, respectively.

Changes in body weight/body weight gain in mice and rats and clinical signs were generally mild. No target organs relevant to human safety were identified and lixisenatide was tolerated in mice and rats at doses up to 4000 µg/kg/day (lixisenatide AUC values >47 times the mean clinical exposure of 7.25 ng·h/mL).

In dogs, reductions in food consumption and body weight loss were dose limiting. Initial dose escalation attenuated the effects of lixisenatide on body weight and food consumption. Using

dose escalation, administration of doses up to 2000 µg/kg/day for 52 weeks was possible. There were no target organs in females. In males, microscopic changes were noted in testes and epididymes in the 13 week study at 200 and 500 µg/kg/day and in the 52 week study at 400 and 2000 µg/kg/day. The changes in the testes included moderate to severe hypospermatogenesis in seminiferous tubules and epididymal dilation, degeneration, and oligospermia, or aspermia and were not present after 4 weeks without treatment at the end of the 13 week study. The changes in testes and epididymes occurred at very high multiples of human exposure (>140 times). The large margins to clinical exposure for effects on testes/epididymes in the dogs, as well as a mechanistic study showing species difference in GLP-1receptor expressions, indicate a very low risk for effects to male patients with the clinical use of lixisenatide.

Carcinogenesis
Carcinogenicity studies were conducted in mice and rats given s.c. lixisenatide doses of 40, 200, and 1000 µg/kg BID for 2 years. In mice, lixisenatide resulted in thyroid gland C-cell adenomas in males at 1000 mcg/kg BID and increased incidences of thyroid focal C-cell hyperplasia in males at 200 mcg/kg BID and males and females given 1000 mcg/kg BID. In rats, there were non dose-dependent increased incidences of thyroid C-cell focal hyperplasia and adenomas at all dose levels and C-cell carcinomas at 200 and 1000 mcg/kg BID in both sexes.

A no-effect dose level for increased thyroid hyperplasia and C-cell adenomas was not identified in rats. Systemic exposure at the low dose in rats was >9-fold when comparing mean AUC values in rats to clinical exposure, while that at the higher doses where C-cell carcinomas were observed was ≥35-fold. In mice, lixisenatide-related thyroid C-cell adenomas were confined to the high dose males given 1000 µg/kg BID, at which exposure was 128 times that in patients. The exposure margin at the 200 µg/kg no effect dose level for tumors was 26-fold. Increased incidences of thyroid C-cell hyperplasia were seen at 200 (males only) and 1000 µg/kg BID, with mouse/human margins at the no effect dose level of 40 µg/kg BID calculated as 4-fold.

Mutagenesis
Lixisenatide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity [Ames], human lymphocyte chromosome aberration, mouse bone marrow micronucleus).

Studies in which male and female rats received twice daily subcutaneous doses lixisenatide of 2, 29, or 414 mcg/kg prior to pairing through gestation day 6 did not indicate any adverse effects on male or female fertility in rats up to the highest dose tested, 414 mcg/kg, or approximately 300 times the clinical systemic exposure at 20 mcg/day based on mcg/m^2.

Embryo fetal development
Lixisenatide transfer across the placenta was limited and effects on embryo fetal development in rats and rabbits were noted in the presence of maternal toxicity. Body weight loss and reduced food consumption may have contributed to the embryo fetal toxicity, but a direct effect cannot be excluded. A relationship of toxicity to the dams on skeletal ossification and fetal growth is generally accepted; however, the correlation to visceral and external malformations is less well supported.

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 µg/kg (5, 70, or 1000 µg/kg/day) from gestation day (GD) 6 to 17 (organogenesis), maternal toxicity was noted at all doses, which consisted of clinical signs and initially dose-dependent decreases in body weight and reduced food consumption. Fetuses showed a dose related trend of retarded growth and retarded ossification. All doses led to single cases of fetal malformations: one

microphthalmia (5 µg/kg/day), one anophthalmia and one diaphragmatic hernia (one fetus each at 70 µg/kg/day), and similar multiple skeletal malformations in one retarded fetus of each dose group. Thus, the NOAEL for embryo fetal toxicity was less than 5 µg/kg/day (AUC < clinical exposure).

In rabbits, there were two embryo fetal development studies. In the high dose study, lixisenatide was administered sc at 5, 50, and 500 µg/kg/day twice daily (approximately 8 h apart) from GD 6 to 18, while in the follow up study, doses were 0.3, 2, and 5 µg/kg/day. Lixisenatide treatment at ≥2 µg/kg/day resulted in decreased motor activity, piloerection, decreased food and water consumption, and initial decreases body weight followed by decreased body weight gain. There was a slight increase in postimplantation loss with a related decrease in the number of live fetuses at 500 µg/kg/day. There was an increase at fetal malformations at ≥5 µg/kg/day (4-times clinical exposure). In the high dose study, there were 5 cases of multiple malformations (2 at 5 µg/kg/day, 2 at 50 µg/kg/day, and 1 at 500 µg/kg/day), as well as single malformations at all doses. There was also a tendency to dose dependent increases in fetuses showing anomalies of the sternebrae, as well as retarded ossification. The NOAEL for maternal toxicity in rabbit was 0.3 µg/kg/day and for embryo-fetal development was 2 µg/kg/day, and at these doses, AUC values were < clinical exposure and 2 times clinical exposure, respectively.

Peri and postnatal development
Lixisenatide was administered to time mated female rats (F0 generation) sc at 4, 40, and 400 µg/kg/day (2, 20, and 200 µg/kg/day BID) from GD 6 to lactation day 21. Clinical signs in dams, initial body weight loss with reduced body weight throughout dosing and reduced food consumption, were seen at all dose levels. Pup mortality was slightly increased and there were severely growth delayed pups with multiple skeletal malformations at 400 µg/kg/day. The number of pups/litter that showed insufficient suckling increased slightly and coat growth showed a slight delay at 40 and 400 µg/kg/day, but there were no other effects on developmental landmarks, sensory function, motor development, memory, learning, and reproductive function of the F1 generation. The NOAEL for effects in the F0 dams was not identified (<4 µg/kg/day), while the NOAEL for toxicity in F1 animals was 4 µg/kg/day. Based on systemic exposure values in pregnant rats extrapolated from toxicokinetic data in the pivotal embryo-fetal development study, exposure at the 400 µg/kg/day dose where malformations were seen was >32-times that in patients while exposure at 4 µg/kg/day was likely sub-therapeutic.

Juvenile Toxicity
Juvenile toxicity studies were conducted in rats and dogs. There were no findings in these studies that were not identified in studies conducted with adult animals or were considered related to reduced body weight and food consumption.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ADLYXINE Solution for injection, 10 mcg/dose and 20 mcg/dose, submission control no. 193862, Product Monograph, sanofi-aventis Canada Inc. (May 23, 2017)

2. LANTUS Solution for injection 100 U/mL, submission control no. 190627, Product Monograph, sanofi-aventis Canada Inc. (April 6, 2016)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SOLIQUA™

Insulin glargine and Lixisenatide injection

Read this carefully before you start taking **SOLIQUA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SOLIQUA**.

Serious Warnings and Precautions

- Low blood sugar (hypoglycemia) is very common with medicines containing insulin such as SOLIQUA.
- When left untreated, hypoglycemia or hyperglycemia (high blood sugar) can cause loss of consciousness, coma, or death.
- Check your blood sugar levels regularly. Your healthcare professional will tell you when and how often to check your blood sugar levels (see "Other warnings you should know about" section below for more information).
- Your healthcare professional will tell you how much insulin you need each day. It is important to use SOLIQUA as prescribed.
- **Do not** inject SOLIQUA into your vein (intravenously) or muscle (intramuscularly).
- **Do not mix SOLIQUA with any other type of insulin or liquid because it might not work as intended.**
- Use SOLIQUA only if the solution inside the pen is clear, colourless and free of particles.

What is SOLIQUA used for?

- SOLIQUA is used along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes. It is usually prescribed when insulin with or without metformin is not enough to control your blood sugar levels.

How does SOLIQUA work?

SOLIQUA contains two diabetes medicines:

- insulin glargine: a long-acting type of insulin which helps control blood sugar (glucose) throughout the day.
- lixisenatide: a medicine that belongs to a class drug called "GLP-1 receptor agonist" . Lixisenatide helps the body produce its own additional insulin when your blood sugar is high. Lixisenatide also slows the absorption of sugar from food.

What are the ingredients in SOLIQUA?

Medicinal ingredients: insulin glargine and lixisenatide

Non-medicinal ingredients: Glycerol, hydrochloric acid/ sodium hydroxide (for pH adjustment), metacresol (2.7 mg/mL; preservative), methionine, water for injection, zinc chloride.

SOLIQUA comes in the following dosage forms:

Sterile solution for injection in a 3 mL prefilled SoloSTAR pen, olive colored.

Each mL of **SOLIQUA** contains:

- 100 units insulin glargine
- 33 mcg lixisenatide

Each unit dialed contains:

- 1 unit insulin glargine
- 0.33 mcg lixisenatide

Do not use SOLIQUA if:

- You are allergic to any of the ingredients in SOLIQUA (see "What are the ingredients in SOLIQUA?" section above)
- You or a member of your family has ever had
    - a thyroid cancer known as medullary thyroid cancer
    - or a hereditary condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- You are pregnant or breastfeeding
- You have type I diabetes
- You have diabetic ketoacidosis (a serious complication of diabetes)
- You are having an episode of hypoglycemia

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SOLIQUA. Talk about any health conditions or problems you may have, including if you:

- have or have had a type of thyroid cancer called medullary thyroid carcinoma or if a family member of yours has had this
- have or have had an inherited condition called multiple endocrine neoplasia syndrome type 2 or if a family member of yours has had this
- have any heart problems such as heart failure or heart rhythm disturbances (fast pulse or irregular heart rhythm, etc.)
- have severe stomach problems such as:
    - gastroparesis (slowed emptying of your stomach)
    - history of stomach surgery
    - conditions that involve inflammation of the gut (ulcerative colitis or Crohn's disease)
- are taking a rapid-acting or short-acting insulin. SOLIQUA has not been studied with this type of insulin
- have or have had pancreatitis (swelling of the pancreas)
- have stones in your gallbladder (gallstones), high levels of fat in your blood (hypertriglyceridemia) or if you abuse alcohol
- have severe kidney problems or if you are on dialysis
- have diabetic retinopathy (condition affecting the eye)
- are 65 years of age or older
- are allergic to other diabetes medicines in the GLP-1 receptor agonist class
- are breast-feeding or plan to breast-feed
- are pregnant or plan to become pregnant
- are younger than 18 years old. SOLIQUA is not recommended for use in children under 18 years of age

Other warnings you should know about:

While using SOLIQUA be aware of the following:

- SOLIQUA may affect your kidneys. Your doctor will do blood tests to monitor how well your kidneys are working before you take SOLIQUA and while you are taking SOLIQUA.
- SOLIQUA can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will discuss the results with you.
- **Seek medical attention right away and stop taking SOLIQUA if** you experience severe pain in your stomach area (abdomen) that will not go away with or without vomiting. This could be a sign of inflamed pancreas (acute pancreatitis).
- SOLIQUA may cause dehydration (loss of fluids from your body) from vomiting and diarrhoea. Drink plenty of fluids to avoid dehydration.
- **Driving and using machines:** hypoglycemia or hyperglycemia (see information below) can affect your ability to drive and use tools or machines. Ask your healthcare professional 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

Hypoglycemia (low blood sugar levels)

Hypoglycemia (too little glucose in the blood) is one of the most common side effects in people using insulin. Serious hypoglycemia may be life-threatening (see Serious Warnings and Precautions Box above). Learn to recognise the signs of hypoglycemia – so you can take action to stop it getting worse.

Reasons why hypoglycemia may happen:

Examples include:

- You inject too much SOLIQUA
- You are not eating on time or you don't eat enough
- You are recovering from an illness, from fever, from an injury, operation or other stress.
- You are doing more exercise than usual or a different type of physical activity
- You are taking or have stopped taking certain other medicines (see section below about other medicines that may interact with SOLIQUA)
- You change the area where you inject SOLIQUA (for example from the thigh to the upper arm)
- You lose carbohydrates from being sick (vomiting) or diarrhoea
- You drink alcohol – especially when you have not eaten much
- You have severe kidney or liver disease, or some other disease such as hypothyroidism

Warning signs of hypoglycemia:

When your blood sugar level falls, you may have signs such as:

- sweating, clammy skin
- feeling anxious
- fast or irregular heartbeat
- high blood pressure
- headaches
- feeling very hungry

- feeling sick (nausea) or being sick (vomiting)
- feeling tired, sleepy, weak
- difficulty concentrating or speaking
- trembling
- tingling in the hands or arms, feeling numb and tingling often around the mouth

Not all signs will be present and some individuals may have other or no signs.

Severe hypoglycemia (very low blood sugar) can make you:

- confused and disoriented
- have seizures.
- lose self-control or pass out

Make sure you always wear your diabetes identification..

When the signs of hypoglycemia 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 a psychiatric illness.
- Your low blood sugar comes on slowly.
- Your low blood sugar is always around “normal” or your diabetes control has greatly improved recently.
- You are taking or have taken certain other medicines (see section below about other medicines that may interact with SOLIQUA).
- You develop hypoglycemia during the night (called “nocturnal hypoglycemia”). It is fairly common and lasts over 4 hours. Because you are usually asleep when it occurs, nocturnal hypoglycemia can go undetected, resulting in increased risk of severe hypoglycemia compared to the daytime. To help reduce the risk of unnoticed signs of night-time hypoglycemia, your doctor may ask you to regularly check your overnight blood glucose levels.

You may not recognize when your blood sugar drops too low. Often the first sign of this is confusion or loss of consciousness. In such cases, you may develop severe hypoglycemia (and even pass out) before you know what is happening. Hypoglycemia can also cause to falls, injuries and motor vehicles accidents. As such, if you find it difficult to recognize your warning signs of hypoglycemia, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycemia.

What to do if you experience hypoglycemia?

- Be familiar with the signs of low blood sugar.
- If you are experiencing signs of a low blood sugar level, check your blood sugar immediately.
- Take about 15 grams of sugar (carbohydrate) straight away. Examples of food or drinks you can use include glucose tablets, sugar (3 packets or 1 tablespoon dissolved in water), honey (1 tablespoon) or a regular soft drink or juice (2/3 cup). Carry a source of fast-acting carbohydrate (such as glucose tablets) with you at all times.
- If your blood sugar drops very low, you may need help from another person. Tell your relatives, friends and close colleagues to get medical help straightaway if you are not

able to swallow or if you pass out (become unconscious). You may require an injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

- If you have hypoglycemia often, have difficulty in recognizing the symptoms, or if your diabetes is getting worse, you should consult your health professional to:
    - adjust your therapy (insulin and/or other medication)
    - adjust meal plans
    - and/or adjust your physical activity
- Talk with your healthcare professional about the complete information you need to know about prevention and how to deal with low blood sugar.

Hyperglycemia (high blood sugar levels)

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Reasons why hyperglycemia 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 eating significantly more than your meal plan suggests.
- 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 below about other medicines that may interact with SOLIQUA).

Warning signs of hyperglycemia:

Hyperglycemia can be mild or severe. It can progress to high glucose levels, diabetic ketoacidosis (DKA), and result in loss of consciousness and death.

Symptoms of hyperglycemia include:

- confusion or drowsiness
- increased thirst
- decreased appetite, nausea, or vomiting
- rapid heart rate
- increased urination and dehydration (too little fluid in your body)
- blurred vision
- flushed dry skin,
- acetone odour of breath
- heavy breathing
- abdominal (stomach area) pain

Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis is a rare but serious, sometimes life-threatening problem you can get with diabetes because of increased levels of “ketone bodies” in your urine or blood, seen in tests.

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and acetone.

Symptoms of diabetic ketoacidosis are similar with the ones listed in the section “Warnings signs of hyperglycemia” above.

What to do if you experience hyperglycemia or DKA:

- Contact your doctor immediately if you have severe hyperglycemia or DKA. This must always be treated by a doctor, normally in a hospital.
- Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional. SOLIQUA should not be used to treat DKA, and the persons treating you should be advised you are taking a long-acting insulin and about your regimen.

Other medicines that may interact with SOLIQUA

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SOLIQUA:

a. Medicines that increase your risk of having low blood sugar (hypoglycemia):
    - Insulin and any other medicine taken by mouth to treat diabetes such as sulfonylurea class of drugs (glyburide, gliclazide and glimepiride etc.)
    - Angiotensin converting enzyme (ACE) inhibitors, for heart problems or high blood pressure
    - Salicylates (such as acetylsalicylic acid) to treat pain and fever
    - Disopyramide, for heart problems.
    - Fibrates, for lowering high levels of blood fats
    - Fluoxetine, for depression
    - Monoamine oxidase inhibitors (MAOIs), for depression or Parkinson´s disease
    - Pentoxifylline used to improve blood flow
    - Propoxyphene, a pain reliever
    - Octreotide to treat severe diarrhea, flushing, etc
    - Sulfonamide antibiotics, to treat infections
b. Medicines that increase your risk of having high blood sugar (hyperglycemia):
    - Corticosteroids such as cortisone and prednisolone, for inflammation.
    - Danazol, for endometriosis.
    - Diazoxide, for high blood pressure.
    - Diuretics (water pills) for high blood pressure
    - Sympathomimetic medicines such as epinephrine (for severe allergy), salbutamol and terbutaline, for asthma
    - Glucagon, for very low blood sugar
    - Isoniazid, for tuberculosis
    - Somatropin, a growth hormone
    - Thyroid hormones, for thyroid problems
    - Oestrogens and progestogens, in birth control control pills
    - Protease inhibitors, for HIV
    - Drugs for mental health problems such as clozapine, olanzapine and phenothiazine derivatives (chlorpromazine, Fluphenazine etc)

c. Medicines that increase your risk of having hypoglycemia or hyperglycemia:
    - Beta-blockers such as propranolol, atenolol or heart problems or high blood pressure
    - Clonidine, for high blood pressure
    - Lithium, for mental health problems
    - Pentamidine for infections
    - Drinking alcohol
d. Medicines that may make it harder to recognise warning signs of low blood sugar: Beta-blockers and some other medicines (such as clonidine, guanethidine, reserpine, for high blood pressure).
e. Medicines that cause or worsen heart failure such as pioglitazone or rosiglitazone (to treat diabetes). SOLIQUA should not be used in combination with these medicines.
f. Medicines that increase your heart rate or that affect your heart rhythm.
g. Warfarin, a blood thinner: You might need to have more frequent blood tests to check your blood clotting.
h. Other medicines taken by mouth. SOLIQUA slows stomach emptying. As such, it may affect the effect of some medicines that you swallow and should not stay too long in your stomach like:
    - Birth control pills: Take these at least 1 hour before your SOLIQUA injection or at least 11 hours after your SOLIQUA injection.
    - Antibiotics: Take these at least 1 hour before your SOLIQUA injection.
    - Acetaminophen (for pain and fever): Take this at least 1 hour before your SOLIQUA injection.
    - Atorvastatin (to lower cholesterol): Take this at least 1 hour before your SOLIQUA injection.

    Ask your healthcare professional when you should take any other medicines that you take by mouth.
i. SOLIQUA with alcohol: Your blood sugar level may either rise or fall if you drink alcohol. Check your blood sugar level more often when you take alcohol.

How to take SOLIQUA:

Before you use SOLIQUA:

- Read the *Instructions for Use* for complete instructions on how to use the SOLIQUA pen and how to inject SOLIQUA.
- Talk to your healthcare professional about how to properly use SOLIQUA before you use it for the first time.
- Use SOLIQUA exactly as prescribed by your doctor.
- Pen needles are not included. Ask your healthcare professional which needles to use.
- **Do not** share SOLIQUA with anyone else, even if you change the needle. You may give another person an infection or get an infection from them.
- Always look through the pen window before each injection. The liquid inside the pen should be clear, colourless, water-like and free of particle. **Do not** use SOLIQUA if liquid inside the pen is discolored, cloudy, contains particles, or if there are any signs of leakage.
- Do not use a syringe to remove SOLIQUA from the pre-filled pen to avoid dosing errors and potential for overdose.

How to inject SOLIQUA:

- Inject SOLIQUA under the skin (subcutaneously) of your upper leg (thigh), stomach area (abdomen) or upper arm.
    - You must change the injection site every day.
    - If you are injecting the same area (thigh, abdomen or upper arm), you must use a different spot.
    - This helps prevent skin changes in the spot where you inject SOLIQUA (see "Serious side effects and what to do about them" table)
- **Do not** inject SOLIQUA into a vein or muscle.

Usual dose:

- Based on your previous insulin use, your healthcare professional will tell you how much SOLIQUA you need each day.
- Your dose of SOLIQUA is administered as 'units'. The dose window on the pen shows the number of units.
- The olive coloured SOLIQUA SoloSTAR pen delivers between 15 and 60 units of SOLIQUA. **Do not** use the SOLIQUA SoloSTAR pen for doses less than 15 units, or higher than 60 units.
- Inject SOLIQUA once a day within one hour before the first meal of the day. Use SOLIQUA at around the same time every day.
- Many factors may affect your usual SOLIQUA dose, which may include changes in your diet, activity, or work schedule. Follow your health professional's instructions carefully. Consult your health professional if you notice your insulin requirements changing markedly.

Overdose:

If you have injected too much SOLIQUA, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. In general, to prevent hypoglycemia you must eat more food and monitor your blood sugar (see "Hypoglycemia" section above).

If you think you have taken too much SOLIQUA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of SOLIQUA, inject the missed dose within the hour prior to the next meal.
- Never take two doses on the same day to make up for a missed dose.
- Do not stop using SOLIQUA without talking to your doctor. If you stop using it, your blood sugar levels can increase.

What are possible side effects from using SOLIQUA?

These are not all the possible side effects you may feel when taking SOLIQUA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- nausea, vomiting
- diarrhea

- cough
- runny or stuffy nose, sneezing
- flu (fever, tiredness, body aches)
- urinary tract infection
- back pain
- headache, dizziness
- muscle pain
- bruising, itching, redness or pain of the injection area
- sore throat
- urethritis (pain with urination)
- nervousness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Hypoglycemia (low blood sugar):** • change in mood • change in vision • confusion, dizziness • fast heartbeat • feeling faint, weakness, shaking • headache, • hunger • sweating See also Hypoglycemia section above.	✓		
RARE			
Changes of skin in the spot where you inject SOLIQUA: • loss of fat under the skin resulting in small dents (lipodystrophy) • buildup of fat below the surface of the skin, causing lumps (lipohypertrophy). Change the injection site with each injection to help prevent these changes		✓	
Severe allergic reactions: • itching, rash all over your body, • shortness of breath, • difficulty breathing or swallowing • fainting • sudden swelling of the face, lips, tongue or throat, rash, very fast heartbeat.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Before first use (unopened pen):

- Store the pen in the refrigerator, between 2°C - 8°C
- Keep the pen the original package to protect from light
- **Do not** freeze
- **Discard the pen if heated or frozen**

After first use (opened/in use pen)

- Store the pen at room temperature (up to 25°C)
- **Do not** put your pen back in the refrigerator
- **Do not** store with needle attached
- Replace the pen cap after use to protect from light
- **Discard the pen 28 days after first use or if heated or frozen**
- Do not use SOLIQUA after the expiration date printed on the label

Keep out of reach and sight of children.

If you want more information about SOLIQUA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sanofi.ca, or by calling 1-888-852-6887

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised: June 22, 2018

INSTRUCTIONS FOR USE

SOLIQUA™ SoloSTAR® (insulin glargine and lixisenatide injection) for subcutaneous injection

Read these instructions carefully before using your SOLIQUA™ SoloSTAR pen.

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

SOLIQUA is an injectable prescription medicine that contains 2 diabetes medicines, insulin glargine and lixisenatide in a SoloStar® pen. The drug combination in this pen is only for the daily injection of 15 to 60 units of SOLIQUA. Each unit dialed contains 1 unit insulin glargine and 0.33 mcg lixisenatide.

Important information

- Check the label on the SOLIQUA SoloSTAR pen each time you give your injection to make sure you are using the correct medicine.
- **Do not** use your pen if it is damaged or if you are not sure that it is working correctly.
- Perform a safety test before each injection (see "**Step 3: Do a safety test"**).
- Always carry a spare pen and spare needles in case they are lost or stop working.
- **Do not reuse needles.** Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection. If you reuse needles, you might not get your dose (underdosing) or get too much (overdosing).
- **Do not** use SOLIQUA in an insulin pump or inject SOLIQUA into your vein (intravenously) or muscle (intramuscularly).
- **Do not** mix SOLIQUA in any other type of insulin or liquid medicine prior to injection.
- Change (rotate) your injection sites within the area you chose with each dose. Do not use the same spot for each injection, to avoid skin thickening or pits at the injection site (lipodystrophy).

Learn to inject

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

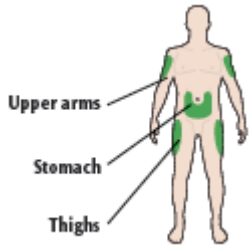
Need help?

If you have any questions about your pen or about diabetes, ask your healthcare provider, go to **www.sanofi.ca** or call sanofi-aventis at **1-888-852-6887**.

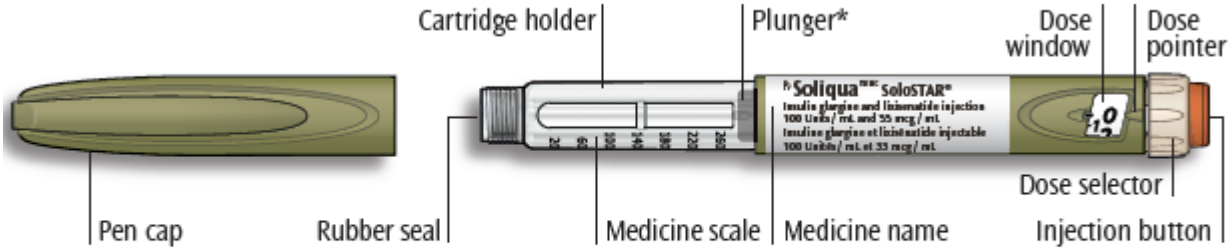
Supplies you will need: Get to know your pen

- 1 SOLIQUA SoloSTAR pen
- 1 new sterile needle (see **Step 2 "Attach a new needle"**)
- 1 alcohol swab
- a puncture-resistant container for used needles and pens (see "**Throwing your pen away"** at the end of these Instructions for Use)

Places to inject



Get to know your pen



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

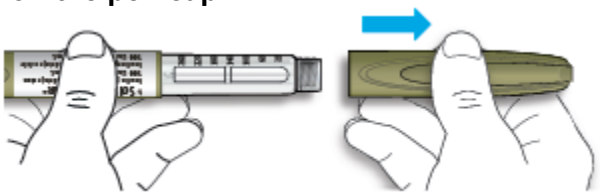
STEP 1: Check your pen

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

1A. Check the name and expiration date on the label of your pen.

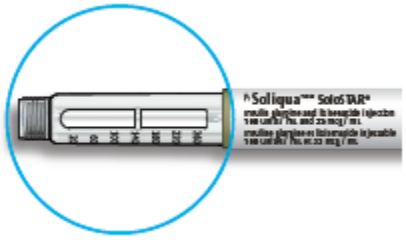
- Make sure you have the correct medicine. This pen is olive coloured with a brown injection button (see the **"Get to know your pen"** diagram).
- **Do not** use your pen after the expiration date on the pen label.

1B. Pull off the pen cap.

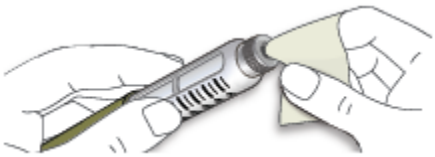


1C. Check that the medicine is clear and to almost colorless.

- **If you see small particles, do not use this pen. Contact your healthcare professional.**



1D. Wipe the rubber seal with an alcohol swab.



If you have other injector pens

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

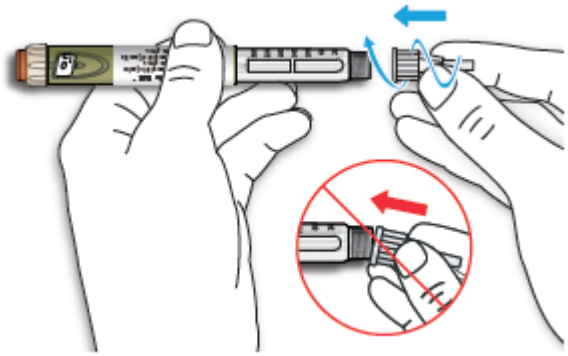
<u>STEP 2: Attach a new needle</u>

Do not reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection.

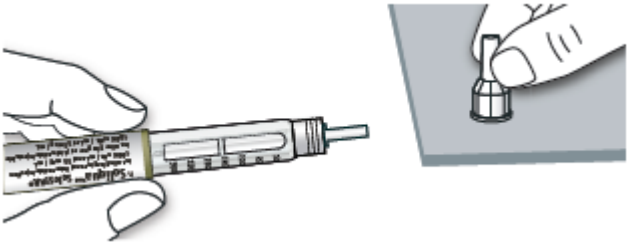
- Only use needles that are meant to be used with SOLIQUA SoloSTAR pen. Needles are supplied separately. If you do not know what needles to use, ask your healthcare provider or pharmacist.

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

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



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



2D. Pull off the inner needle cap and throw it away.

Handling needles

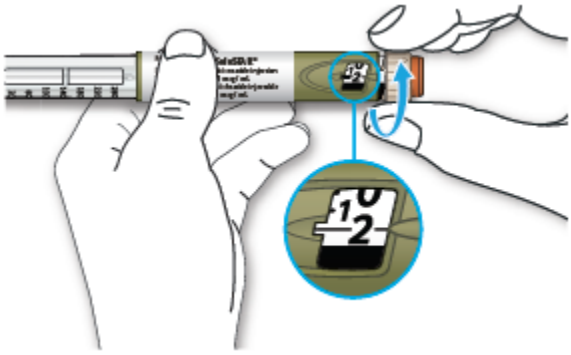
- Take care when handling needles to prevent needle-stick injury and cross-infection.

STEP 3: Do a safety test

Perform a safety test before each injection to:

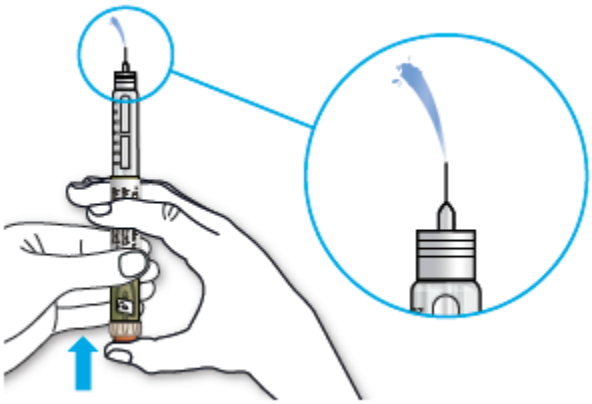
- Check your pen and the needle to make sure they are working properly.
- Make sure that you get the correct dose.

3A. Select 2 units by turning the dose selector until the dose pointer is at the 2 mark.



3B. Press the injection button all the way in.

- When the medicine 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 the medicine.
- If no medicine comes out after the third time, the needle may be blocked. If this happens:
  - change the needle (**see Step 6** to remove the needle **and Step 2** to attach a new needle),
  - then repeat the safety test **(see Step 3A).**
- **Do not** use your pen if still no medicine comes 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

Do not select a dose or press the injection button without a needle attached. This may damage your pen.

- **Only use this pen to inject your daily dose from 15 to 60 units. Do not change your dose unless your healthcare provider has told you to change your dose.**
- **Do not** use this pen if you need a single daily dose that is more than 60 units.
- **Do not** use the pen if your single daily dose is less than 15 units.

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

4B. Turn the dose selector until the dose pointer lines up with your dose.

- Do not dial your dose by counting the clicks, because you might dial the wrong dose. Always check the number in the dose window to make sure you dialed the correct 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.

How to read the dose window

- Each line in the dose window equals 1 unit of SOLIQUA.
- Even numbers are shown in line with the dose pointer, as shown in picture

30 units selected

- Odd numbers are shown as a line between even numbers, as shown in picture.

29 units selected

Units of medicine in your pen

- This pen contains 300 units of SOLIQUA and it is intended to be used for more than one dose.

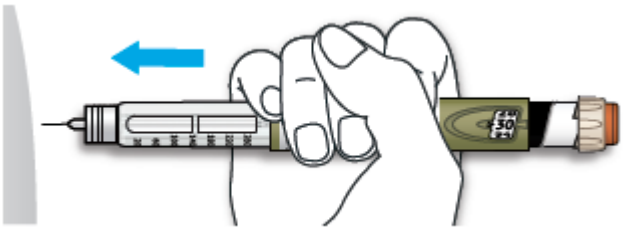
STEP 5: Inject your dose

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

5A. Choose a place to inject as shown in the picture labeled "Places to inject."

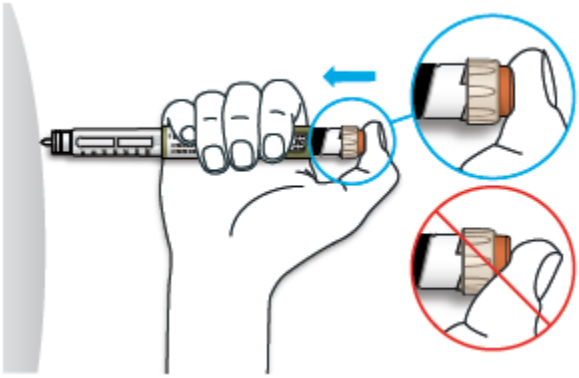
5B. Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



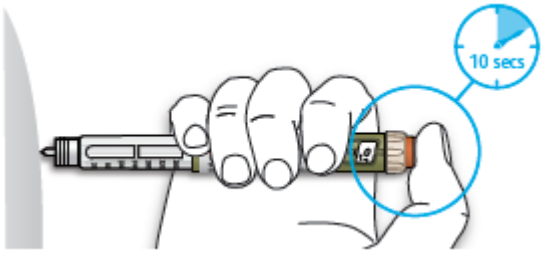
5C. Place your thumb on the injection button. Then press all the way in and hold.

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



5D. 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.



5E. 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** to remove the needle and **Step 2** to 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.

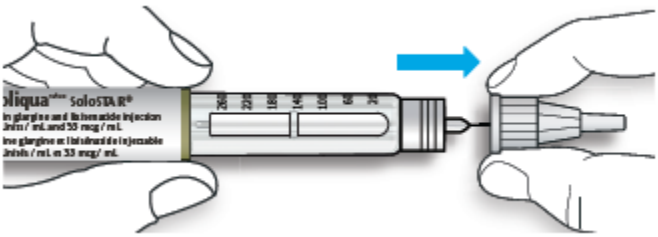
STEP 6: Remove the needle

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

- Do not put the inner needle cap back on.

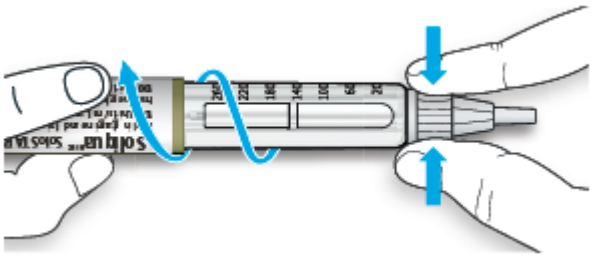
6A. Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.

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



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

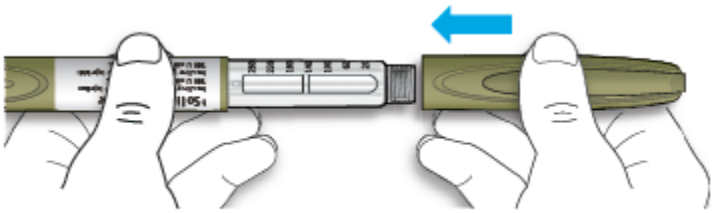
- Try again if the needle does not come off the first time.



6C. Throw away the used needle in a puncture-resistant container (see "Throwing your pen away" at the end of these Instructions for Use).

6E. 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 day**s 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. If you accidently freeze your pen, throw it away.

After first use

- Keep your pen at room temperature, **up to 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.

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

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

Replace the pen cap before disposing of your SOLIQUA SoloSTAR pen.

- Put the used SOLIQUA SoloSTAR pen in a sharps container right away after use. Do not dispose of the SOLIQUA SoloSTAR pen in your household trash.
- If you do not have a sharps container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labelled to warn of hazardous waste inside the container.

Such containers should be sealed and disposed of properly.

If you have any questions about SOLIQUA or about diabetes, ask your healthcare professional or call sanofi-aventis Canada Inc. at **1-888-852-6887**.

Manufactured by sanofi -aventis Canada Inc.,
Laval, Quebec, Canada H7V 0A3

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