Professional information for SOLIQUA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SOLIQUA 33/100, 33 µg/mL and 100 units/mL, solution for injection

SOLIQUA 50/100, 50 µg/mL and 100 units/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of SOLIQUA 33/100 pre-filled pen contains 33 µg lixisenatide and 3,64 mg insulin glargine (equivalent to 100 units insulin glargine), 2,7 mg of the preservative metacresol, and 0,0626 mg of zinc chloride as stabiliser. One pre-filled pen contains 3 mL equivalent to 100 µg lixisenatide and 300 units insulin glargine. One unit of SOLIQUA 33/100 contains 0,33 µg of lixisenatide and 1 unit of insulin glargine.

Each mL of SOLIQUA 50/100 pre-filled pen contains 50 µg lixisenatide and 3,64 mg insulin glargine (equivalent to 100 units insulin glargine), 2,7 mg of the preservative metacresol, and 0,0626 mg of zinc chloride as stabiliser. One pre-filled pen contains 3 mL equivalent to 150 µg lixisenatide and 300 units insulin glargine. One unit of SOLIQUA 50/100 contains 0,5 µg of lixisenatide and 1 unit of insulin glargine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

SOLIQUA is available as a sterile, clear and colourless solution for injection. No particulate matter

is visible.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLIQUA is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when oral glucose-lowering medicines alone or combined with basal insulin, or basal insulin alone, do not provide adequate glycaemic control.

4.2 Posology and method of administration

SOLIQUA is titratable and available in two pens, providing different dosing options.

The differentiation between the pen strengths is based on the dose range of the pen:

- SOLIQUA 50/100 (10 – 40 pen):
  - 1 unit of SOLIQUA contains 0,5 µg lixisenatide and 1 unit of insulin glargine
  - Allows daily doses between 10 and 40 units of SOLIQUA (10 to 40 units of insulin glargine in combination with 5 to 20 µg lixisenatide)
- SOLIQUA 33/100 (30 – 60 pen):
  - 1 unit of SOLIQUA contains 0,33 µg lixisenatide and 1 unit of insulin glargine
  - Allows daily doses between 30 and 60 units of SOLIQUA (30 to 60 units insulin glargine in combination with 10 to 20 µg lixisenatide).

To avoid medicine errors, make sure the correct SOLIQUA pen, (10 – 40) pen or (30 – 60) pen, is stated in the prescription.

The maximum daily dose of SOLIQUA is 60 units of SOLIQUA (60 units insulin glargine and 20 µg lixisenatide).

SOLIQUA should be administered subcutaneously once a day within 1 hour prior to any meal.

Posology

The dose of SOLIQUA must be individualised based on clinical response and is titrated based on the patient's need for insulin.

The lixisenatide dose is increased or decreased along with insulin glargine dose and also depends on which pen is used.

Patients adjusting the amount or timing of dosing with SOLIQUA should only do so under medical guidance with appropriate glucose monitoring.

Initiation of SOLIQUA

Starting dose of SOLIQUA

Treatment with basal insulin or glucagon-like peptide-1 (GLP-1) receptor agonist or oral glucose-lowering medicine should be discontinued prior to initiation of SOLIQUA.

The starting dose of SOLIQUA is selected based on previous anti-diabetic treatment and in order not to exceed the recommended lixisenatide starting dose of 10 µg:

Table 1. Starting dose of SOLIQUA

<table>
<tr><td colspan="2"></td><td colspan="4">Previous treatment</td></tr>
<tr><td></td><td></td><td>Insulin naïve patients (Oral anti-diabetic treatment or GLP-1 receptor agonist)</td><td>Insulin glargine (100 units/mL)** < 20 units</td><td>Insulin glargine (100 units/mL)** ≥ 20 to < 30 units</td><td>Insulin glargine (100 units/mL)** ≥ 30 to ≤ 60 units</td></tr>
<tr><td rowspan="2">Starting dose and Pen</td><td>SOLIQUA 50/100 (10 – 40) pen</td><td colspan="2">10 units (10 units/5 µg)*</td><td>20 units (20 units /10 µg)*</td><td></td></tr>
<tr><td>SOLIQUA</td><td colspan="3"></td><td>30 units</td></tr>
</table>

	33/100 (30 – 60) pen		(30 units /10 µg)*

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

** If a different basal insulin was taken:

- For twice daily basal insulin or insulin glargine (300 units/mL), the total daily dose previously used should be reduced by 20,0 % to choose the SOLIQUA starting dose.
- For any other basal insulin, the same rule as for insulin glargine (100 units/mL) should be applied.

Dosage titration of SOLIQUA

SOLIQUA is to be dosed in accordance with the individual patient's needs for insulin.

It is recommended to optimise glycaemic control via dose adjustment based on fasting self-monitored plasma glucose.

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

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

Special populations

Children

The safety and effectiveness of SOLIQUA in paediatric patients below the age of 18 years have not been established.

Elderly patients (≥ 65 years old)

SOLIQUA can be used in elderly patients. Dose should be adjusted on an individual basis, based

on glucose monitoring. The therapeutic experience in patients ≥ 75 years of age is limited.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of SOLIQUA has not been studied. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity of gluconeogenesis and reduced insulin metabolism. Frequent glucose monitoring and dose adjustment of SOLIQUA may be necessary in patients with hepatic impairment.

Renal impairment

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

Method of administration

Administration is a subcutaneous injection in either the abdomen, deltoid or thigh.
The injection site should be rotated within the same region (abdomen, deltoid or thigh) from one injection to the next to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8). Do not inject into areas of lipodystrophy and cutaneous amyloidosis.

4.3 Contraindications

SOLIQUA is contraindicated in:

- patients with known hypersensitivity to lixisenatide, insulin glargine or to any of the other ingredients listed in section 6.1
- during episodes of hypoglycaemia
- acute pancreatitis
- severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease

- pregnancy and/or lactation (see section 4.6).

4.4 Special warnings and precautions for use

Use of SOLIQUA

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

Risk of pancreatitis

Use of glucagon-like peptide-1 (GLP-1) receptor agonists, as in SOLIQUA, have been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain.
If pancreatitis is suspected, SOLIQUA should be discontinued; if acute pancreatitis is confirmed, SOLIQUA should not be restarted (see section 4.3). Use with caution in patients with a history of pancreatitis.

Lipodystrophy and cutaneous amyloidosis

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

Hypoglycaemia

Hypoglycaemia was the most frequently reported observed undesirable adverse reaction during treatment with SOLIQUA. Hypoglycaemia may occur if the dose of SOLIQUA is higher than required.

Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and

may necessitate dose adjustment. These factors include:

- change in the injection area
- improved insulin sensitivity (e.g. by removal of stress factors)
- unaccustomed, increased or prolonged physical activity
- undercurrent illness (e.g. vomiting, diarrhoea)
- inadequate food intake
- missed meals
- alcohol consumption
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency)
- concomitant treatment with certain other medicines (see section 4.5)
- lixisenatide and/or insulin in combination with a sulfonylurea may result in an increased risk of hypoglycaemia. Therefore SOLIQUA should not be given in combination with a sulfonylurea.

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

Acute gallbladder disease

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

Use in patients with severe gastroparesis

The use of GLP-1 receptor agonists is associated with gastrointestinal adverse reactions. SOLIQUA has not been studied in patients with severe gastrointestinal diseases, including severe gastroparesis, and therefore, the use of SOLIQUA is not recommended in these patients.

Renal impairment

There is no therapeutic experience in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease. The use of SOLIQUA is not recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 4.3).

Concomitant use with other medicines

The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicines.

SOLIQUA should be used with caution in patients receiving oral medicines that require rapid gastrointestinal absorption, careful clinical monitoring or have a narrow therapeutic ratio.

Dehydration

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

Antibody formation

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

The presence of such antibodies may necessitate adjustment of the SOLIQUA dose in order to correct a tendency for hyper- or hypoglycaemia.

Excipients with known effect

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

SOLIQUA contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

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

Insulin glargine

Substances that may increase the blood glucose lowering effect and susceptibility to hypoglycaemia: oral antidiabetics; ACE inhibitors; salicylates; disopyramide; fibrates; fluoxetine; MAO inhibitors; pentoxifylline; propoxyphene; sulphonamide antibiotics.

Substances that may reduce the blood glucose-lowering effect: corticosteroids, danazol, diazoxide, diuretics, sympathomimetic agents (e.g. adrenaline [epinephrine], salbutamol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, oestrogens and progestogens (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicines (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood glucose-lowering effect of SOLIQUA.
Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.
In addition, under the influence of sympatholytic medicines such as beta-blockers, clonidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

Lixisenatide

Lixisenatide is a peptide and is not metabolised by cytochrome P450.
In *in vitro* studies, lixisenatide did not affect the activity of cytochrome P450 isozymes or human transporters tested.

Effect of gastric emptying on oral medicines

Lixisenatide delays gastric emptying which may reduce the rate of absorption of orally administered

medicines.

Use caution when co-administering oral medicines with a narrow therapeutic ratio or that require careful clinical monitoring.

If such medicines are to be administered with food, patients should be advised to take them with a meal or snack when lixisenatide is not administered.

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

Paracetamol

Paracetamol was used as a model medicine to evaluate the effect of lixisenatide gastric emptying.

Lixisenatide 10 µg did not change the overall exposure (AUC) of paracetamol following administration of a single dose of paracetamol 1 000 mg, whether before or after lixisenatide.

No effects on paracetamol C_{max} and t_{max} were observed when paracetamol was administered 1 hour before lixisenatide.

When administered 1 or 4 hours after 10 µg lixisenatide, C_{max} of paracetamol was decreased by 29 % and 31 %, respectively, and median t_{max} was delayed by 2 and 1,75 hours, respectively.

Based on these results, no dose adjustment for paracetamol is required.

Oral contraceptives

Following administration of a single dose of an oral contraceptive medicine (ethinylestradiol 0,03 mg/levonorgestrel 0,15 mg) 1 hour before or 11 hours after 10 µg lixisenatide, the C_{max}, AUC, t½ and t_{max} of ethinylestradiol and levonorgestrel were unchanged.

Administration of the oral contraceptives 1 hour or 4 hours after lixisenatide did not affect AUC and t½ of ethinylestradiol and levonorgestrel, whereas C_{max} of ethinylestradiol was decreased by 52 % and 39 %, respectively, and C_{max} of levonorgestrel was decreased by 46 % and 20 %, respectively and median t_{max} was delayed by 1 to 3 hours.

Based on these results, no dose adjustment for oral contraceptives is required.

It is recommended that oral contraceptives be administered at least 1 hour before or at least 11 hours after SOLIQUA administration.

Atorvastatin

When lixisenatide 20 µg and atorvastatin 40 mg were co-administered in the morning for 6 days, the exposure of atorvastatin was not affected, while C_{max} was decreased by 31 % and t_{max} was delayed by 3,25 hours.

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

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

However, because of the delay in t_{max}, patients taking atorvastatin should be advised to take atorvastatin at least 1 hour before or 11 hours after SOLIQUA administration.

Warfarin and other coumarin derivatives

After concomitant administration of warfarin 25 mg with repeated dosing of lixisenatide 20 µg, there were no effects on AUC and INR (international normalised ratio) while C_{max} was reduced by 19 % and t_{max} was delayed by 7 hours.

Based on these results, no dose adjustment is required for warfarin when co-administered with SOLIQUA.

Digoxin

After concomitant administration of lixisenatide 20 µg and digoxin 0,25 mg at steady state, the AUC of digoxin was not affected.

The t_{max} of digoxin was delayed by 1,5 hours and the C_{max} was reduced by 26 %.

Based on these results, no dose adjustment for digoxin is required when co-administered with SOLIQUA.

Ramipril

After concomitant administration of lixisenatide 20 µg and ramipril 5 mg for 6 days, the AUC of ramipril was increased by 21 % while the C_{max} was decreased by 63 %.

The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2,5 hours. Based on these results, no dose adjustment for ramipril is required when co-administered with SOLIQUA.

4.6 Fertility, pregnancy and lactation

Pregnancy

SOLIQUA is contraindicated during pregnancy (see section 4.3).

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

Lactation

SOLIQUA is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

SOLIQUA has no or negligible influence on the ability to drive a vehicle or use machines.

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

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

4.8 Undesirable effects

The SOLIQUA phase 3 clinical studies included 834 patients treated with SOLIQUA.

The most frequently reported undesirable side effects during treatment with SOLIQUA were hypoglycaemia and gastrointestinal side effects.

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 % and < 10 %; Uncommon ≥ 0,1 % and < 1 %; Rare ≥ 0,01 % and < 0,1 %; Very rare < 0,01 %; Unknown (cannot be estimated from available data).

Infections and infestations:

Uncommon: nasopharyngitis, upper respiratory tract infection

Immune system disorders:

Uncommon: urticaria

Metabolism and nutrition disorders:

Very common: hypoglycaemia

Nervous system disorders:

Common: dizziness

Uncommon: headache

Gastrointestinal disorders:

Common: nausea, diarrhoea, vomiting

Uncommon: dyspepsia, abdominal pain

Rare: delayed gastric emptying

Not known: intestinal obstruction

Skin and subcutaneous tissue disorders:

Not known: cutaneous amyloidosis, lipodystrophy

General disorders and administration site conditions:

Uncommon: fatigue, injection site reactions.

Hypoglycaemia:

Severe hypoglycaemia attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic 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 side effects (nausea, vomiting and diarrhoea) were frequently reported side effects during the treatment period.

In patients treated with SOLIQUA, the incidence of related nausea, diarrhoea and vomiting was 8,4 %, 2,2 % and 2,2 %, respectively. Gastrointestinal side effects were mostly mild and transient in nature. In patients treated with lixisenatide, the incidence of related nausea, diarrhoea and vomiting was 22,3 %, 3,0 % and 3,9 %, respectively.

Skin and subcutaneous tissue disorders:

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

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

4.4).

Immune system disorders:

Allergic reactions (urticarial) possibly related to 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.

Immunogenicity:

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

The incidence of formation of anti-insulin glargine antibodies was 21 % and 26,2 %. In approximately 93 % of the patients, anti-insulin glargine antibodies showed cross-reactivity to human insulin. The incidence of formation of anti-lixisenatide antibodies was approximately 43 %. Neither status for anti-insulin glargine antibodies nor for anti-lixisenatide antibodies had a clinically relevant impact on safety or efficacy.

Injection site reactions:

Some patients taking insulin-containing therapy, including SOLIQUA, have experienced erythema, local oedema, and pruritus at the site of injection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of SOLIQUA is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Side effects can be reported directly to Sanofi's Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Symptoms:

Hypoglycaemia and gastrointestinal side effects 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 hypoglycaemia.

Lixisenatide:

During clinical studies an increased incidence of gastrointestinal disorders was observed.

Management:

Insulin glargine:

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dosage, meal patterns, or exercise may be needed. More severe episodes culminating in coma, seizure, or neurological impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.13 Others

Pharmacotherapeutic groups: Drugs used in diabetes, insulins and analogues for injection, long-acting

ATC code: A10AE54

Insulin glargine:

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

Lixisenatide:

Lixisenatide is a glucagon-like peptide (GLP-1) receptor agonist.

The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas.

The action of lixisenatide is mediated via a specific interaction with GLP-1 receptors, including those on pancreatic alpha and beta cells.

After a meal, lixisenatide activates the following individual physiological responses:

- enhances insulin secretion by beta cells
- slows gastric emptying
- suppresses glucagon secretion by alpha cells.

Lixisenatide stimulates glucose-dependent insulin secretion.

In parallel, glucagon secretion is suppressed.

Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose is absorbed and appears in the circulation.

5.2 Pharmacokinetic properties

The insulin glargine/lixisenatide ratio has no relevant impact on the pharmacokinetics of insulin glargine in SOLIQUA.

Compared to administration of lixisenatide alone, the C_{max} is lower whereas the AUC is comparable

when administered as SOLIQUA. The observed differences in the pharmacokinetics 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 mellitus, insulin glargine showed no pronounced peak.

After subcutaneous administration of insulin glargine/lixisenatide combinations to patients with type 1 diabetes mellitus, the median t_{max} of lixisenatide was in the range of 2,5 – 3 hours.

There was a decrease in C_{max} of lixisenatide of 22 – 34 % compared with separate simultaneous administration of insulin glargine and lixisenatide, which is not likely to be clinically significant.

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

Distribution:

Lixisenatide has a 55 % binding level to human proteins.

Metabolism and elimination:

Insulin glargine:

A metabolism study in humans who received insulin glargine alone indicates that insulin glargine is partly metabolised 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 insulin glargine and degradation products are also present in the circulation.

Lixisenatide:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrated hydrochloric acid (for pH adjustment)

Glycerol 85 %

Metacresol

Methionine

Sodium hydroxide (for pH adjustment)

Water for injection

Zinc chloride.

6.2 Incompatibilities

SOLIQUA must not be mixed with other medicines.

6.3 Shelf life

Unopened (not in-use) pens: 36 months.

Opened (in-use) pens: 28 days.

6.4 Special precautions for storage

Unopened (not in-use) pens:

Store between 2 °C and 8 °C (in refrigerator).

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 at or below 25 °C.

Do not refrigerate.

Do not freeze.

Do not store with attached needle.

Store pen away from direct heat or direct light. The pen cap must be put back on the pen after each injection in order to protect from light.

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

6.5 Nature and contents of container

SOLIQUA 33/100 disposable pen: 3 mL type I, clear and colourless glass cartridge closed with an aluminium flanged cap with punched isoprene rubber, grey laminated sealing disk and a black bromobutyl rubber plunger stopper. It is assembled in an olive-coloured pen-injector with a brown injection button.

SOLIQUA 50/100 disposable pen: 3 mL type I, clear and colourless glass cartridge closed with an aluminium flanged cap with punched isoprene rubber, grey laminated sealing disk and a black bromobutyl rubber plunger stopper. It is assembled in a peach-coloured pen-injector with an orange injection button.

The pen-injector is a disposable device combined with a cartridge that is used to dispense variable doses of SOLIQUA. The design of the pen-injector is based on the already marketed SoloStar® pen-injector, with modifications comprising of the colour of the bodies, caps, injection buttons, and dose selectors as well as the scale on the number sleeves and the dose stop for the maximum dispensable doses.

Pack sizes: 1, 3 or 5 pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect SOLIQUA before each use. SOLIQUA must only be used if the solution is clear, colourless,

with no particles visible.

Since SOLIQUA is a solution, it does not require resuspension before use. Before first use, the pen must be stored at room temperature for 1 to 2 hours.

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

Empty pens must never be reused and must be properly discarded.

The label must always be checked before each injection to avoid medicine errors between SOLIQUA and other injectable antidiabetic medicines, including the two different pens of SOLIQUA (see section 6.5).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBERS

SOLIQUA 33/100: 52/32.16/0149 (Master)

SOLIQUA 50/100: 52/32.16/0150 (Master)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

SOLIQUA 33/100: 24 November 2020

SOLIQUA 50/100: 24 November 2020

10. DATE OF REVISION OF THE TEXT