NEW ZEALAND DATA SHEET – SOLIQUA SOLOSTAR (INSULIN GLARGINE AND LIXISENATIDE)

1 NAME OF THE MEDICINE

Soliqua SoloStar 100 units/mL insulin glargine and 50 micrograms/mL lixisenatide solution for injection

Soliqua SoloStar 100 units/mL insulin glargine and 33 micrograms/mL lixisenatide solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soliqua SoloStar is available in two SoloStar pre-filled disposable pen injectors containing 3 mL of solution.

Each pre-filled pen (peach colour) contains 300 units of insulin glargine and 150 micrograms lixisenatide. Each unit of Soliqua SoloStar contains 1 unit of insulin glargine (100 units/mL) and 0.5 micrograms lixisenatide.

Each pre-filled pen (olive colour) contains 300 units of insulin glargine and 100 micrograms lixisenatide. Each unit of Soliqua SoloStar contains 1 unit of insulin glargine (100 units/mL) and 0.33 micrograms lixisenatide.

Insulin glargine is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Soliqua SoloStar is a sterile clear colourless solution of insulin glargine (100 units/mL) and lixisenatide in titratable fixed ratio doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Soliqua SoloStar is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Soliqua SoloStar should be administered subcutaneously once a day, within 1 hour prior to the first meal each day.

General

Soliqua SoloStar 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.

10 to 40 pre-filled pen (peach colour) Ratio of 2 units: 1micrograms	**30 to 60 prefilled pen (olive colour) Ratio 3 units: 1micrograms**
100 units/mL insulin glargine 50 micrograms/mL lixisenatide	100 units/mL insulin glargine 33 micrograms/mL lixisenatide
1 unit of Soliqua SoloStar contains: 1 unit of insulin glargine (100 units/mL) 0.5 micrograms lixisenatide	1 unit of Soliqua SoloStar contains: 1 unit of insulin glargine (100 units/mL) 0.33 micrograms lixisenatide
Daily Dosing Range: 10 to 40 units insulin glargine 5 to 20 micrograms lixisenatide	Daily Dosing Range: 30 to 60 units insulin glargine 10 to 20 micrograms lixisenatide

To avoid medication errors, make sure the correct Soliqua SoloStar pen, (10-40) pen or (30-60) pen, is stated in the prescription (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The maximum daily dose of Soliqua SoloStar is 60 units available in olive pen (60 units insulin glargine and 20 micrograms lixisenatide)

The dose of Soliqua SoloStar 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 SoloStar, should only do so under medical supervision with appropriate glucose monitoring (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Use in combination with sulphonylurea, glinide, prandial insulin, thiazolidinedione, DDP-4 inhibitor or SGLT-2 inhibitor has not been studied.

Before first use

Inspect Soliqua SoloStar before each use. Soliqua SoloStar must only be used if the solution is clear, colourless, with no particles visible. Since Soliqua SoloStar is solution, it does not require resuspension before use.

Before first use, the pen must be stored at room temperature for 1 to 2 hours. 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 SoloStar and other injectable antidiabetic medicinal products, including the 2 different pens of Soliqua SoloStar (see GENERAL)

Before using Soliqua SoloStar, the instruction for use included in the package leaflet must be read carefully.

Starting dose of Soliqua SoloStar

Maximum recommended starting dose of Soliqua SoloStar is 20 units of insulin glargine for (10-40 pen) and 30 units of insulin glargine for (30-60 pen) in order not to exceed the recommended lixisenatide starting dose of 10 micrograms: see Table 1 below.

Table 1 - Starting dose of Soliqua SoloStar

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="4">Previous treatment</th></tr>
<tr><th>Oral Anti-Diabetic medications (insulin naïve patients)</th><th>Insulin glargine (100 units/mL)** <20 Units</th><th>Insulin glargine (100 units/mL)** ≥20 to <30 Units</th><th>Insulin glargine (100units/mL)** ≥30 to ≤60 Units</th></tr>
<tr><td rowspan="2">Starting dose and pen</td><td>Soliqua SoloStar (10-40) pen[#] “Peach colour”</td><td colspan="2">10 Units of Soliqua SoloStar (10 Units/5 micrograms)*</td><td>20 Units of Soliqua SoloStar (20 Units/10 micrograms)*</td><td></td></tr>
<tr><td>Soliqua SoloStar (30-60) pen [##] “olive colour”</td><td colspan="3"></td><td>30 Units of Soliqua SoloStar (30 Units/10 micrograms)*</td></tr>
</table>

#100units/mL insulin glargine and 50micrograms lixisenatide
##100 units/mL insulin glargine and 33micrograms lixisenatide
*units insulin glargine (100units/mL) /micrograms lixisenatide

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

- For twice daily basal insulin or insulin glargine (300 units/mL), the total daily dose previously taken should be reduced by 20% to choose the Soliqua SoloStar starting dose.

- For any other basal insulin the same rule as for insulin glargine (100 units/mL) should be applied

Dosage titration of Soliqua SoloStar

Soliqua SoloStar 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 plasma glucose (see Pharmacodynamic Effects).

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

- If the patient starts with the Soliqua SoloStar (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 SoloStar (30-60) pen.
- If the patient starts with the Soliqua SoloStar (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 SoloStar. Insulin glargine in combination with other glucose lowering products should be considered for patients requiring >60 units/day of Soliqua SoloStar.

Method of Administration

Administration is a subcutaneous injection in either the abdomen, upper arm or thigh.

The injection sites should be rotated within the same region (abdomen, upper arm or thigh) from one injection to the next to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy and localised cutaneous amyloidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS).

4.3 CONTRAINDICATIONS

Soliqua SoloStar must not be used in patients hypersensitive to insulin glargine, lixisenatide or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Patients, and if appropriate, their relatives, must have received education on T2DM and self-monitoring of blood glucose and have a plan for managing high or lower blood glucose levels.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localised 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 (See Section 4.8 ADVERSE EFFECTS.

Hypoglycaemia

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

Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These factors include:

- inadequate food intake
- missed meals
- alcohol consumption
- lixisenatide and/or insulin in combination with a sulphonylurea may result in an increased risk of hypoglycaemia.
- change in the injection area
- improved insulin sensitivity (e.g. by removal of stress factors)
- unaccustomed, increased or prolonged physical activity
- intercurrent illness (e.g. vomiting, diarrhoea)
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency)
- concomitant treatment with certain other medicinal products (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The dose of Soliqua SoloStar must be individualised based on clinical response and is titrated based on the patient’s need for insulin (see section 4.5 DOSAGE AND METHOD OF ADMINISTRATION).

As with other basal insulins products, the prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

Acute Pancreatitis

Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with lixisenatide although a causal relationship has not been established. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Soliqua SoloStar should be discontinued; if acute pancreatitis is confirmed, lixisenatide should not be restarted. The use of Soliqua SoloStar is not recommended in patients with a history of pancreatitis.

Severe Gastrointestinal Disease

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. Soliqua SoloStar has not been studied in patients with severe gastrointestinal disease, including gastroparesis and therefore, the use of Soliqua SoloStar is not recommended in these patients.

Use in Renal Impairment

There is no therapeutic experience in patients with severe renal impairment (Chronic Kidney Disease (CKD) stages 4-5; creatinine clearance less than 30 mL/min) or end-stage renal disease. Use is not recommended in patients with severe renal impairment or end-stage renal disease.

In patients with mild to moderate renal impairment using Soliqua SoloStar, frequent glucose monitoring and dose-adjustment may be necessary. (See SPECIAL POPULATION).

Concomitant Medicinal Products

The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Soliqua SoloStar should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products are given in section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Dehydration

Patients treated with Soliqua SoloStar 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 SoloStar may cause formation of antibodies against insulin glargine and/or lixisenatide. In rare cases, the presence of such antibodies may necessitate adjustment of the Soliqua SoloStar dose in order to correct a tendency for hyper- or hypoglycaemia. (see section 4.8 ADVERSE EFFECTS).

Medication Error Prevention

Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between 2 different strengths of Soliqua SoloStar and mix-ups with other injectable diabetes medicinal products.

To avoid dosing errors and potential overdose, never use a syringe to draw the product from the cartridge in the pre-filled pen.

Populations not studied

Switch data from GLP-1 receptor agonist to Soliqua SoloStar is not yet available. Soliqua SoloStar has not been studied in combination with DPP-4 inhibitors, sulfonylureas, glinides, pioglitazone and SGLT-2 inhibitors.

Use in the elderly (≥ 65 years old)

Soliqua SoloStar can be used in elderly patients. The dose should be adjusted on an individual basis, based on glucose monitoring. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. For lixisenatide no dose adjustment is required based on age. The therapeutic experience of Soliqua SoloStar in patients ≥75 years of age is limited.

Paediatric use

Safety and effectiveness of Soliqua SoloStar have not been established in paediatric patients.

Effects on laboratory tests

No studies on the effects of Soliqua SoloStar on laboratory tests have been performed.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies with Soliqua SoloStar have been performed.

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

Insulin Glargine

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

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia

Oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect

Corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oral contraceptives, phenothiazine derivatives, somatotrophin, sympathomimetic agents (eg epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (eg olanzapine and clozapine). Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may be sometimes followed by hyperglycaemia.

Others

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation induced by hypoglycaemia 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 at therapeutically relevant concentrations.

Effect of Gastric Emptying on Oral Medications

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

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

Paracetamol (Acetaminophen)

Paracetamol was used as a model medicinal product to evaluate the effect of lixisenatide on gastric emptying. Lixisenatide 10 micrograms did not change the overall exposure (AUC) of acetaminophen following administration of a single dose of acetaminophen 1000 mg, whether before or after lixisenatide. No effects on acetaminophen C_{max} and t_{max} were observed when

acetaminophen was administered 1 hour before lixisenatide. When administered 1 or 4 hours after 10 micrograms lixisenatide, C_{max} of acetaminophen was decreased by 29% and 31% respectively and median t_{max} was delayed by 2.0 and 1.75 hours, respectively. Based on these results, no dose adjustment for acetaminophen is required.

Oral contraceptives

Following administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after 10 micrograms lixisenatide, the C_{max}, AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel were unchanged.

Administration of the oral contraceptive 1 hour or 4 hours after lixisenatide did not affect AUC and $t_{1/2}$ of ethinylestradiol and levonorgestrel, whereas C_{max} of ethinylestradiol was decreased by 52% and 39% respectively and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively and median t_{max} was delayed by 1 to 3 hours.

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

Atorvastatin

When lixisenatide 20 micrograms and atorvastatin 40 mg were coadministered in the morning for 6 days, the exposure of atorvastatin was not affected, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours. No such increase for t_{max} was observed when atorvastatin was administered in the evening and lixisenatide in the morning but the AUC and C_{max} of atorvastatin were increased by 27% and 66% respectively.

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

Warfarin and other coumarin derivatives

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

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

Digoxin

After concomitant administration of lixisenatide 20 micrograms and digoxin 0.25 mg at steady state, the AUC of digoxin was not affected. The t_{max} of digoxin was delayed by 1.5 hour and the C_{max} was reduced by 26%.

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

Ramipril

After concomitant administration of lixisenatide 20 micrograms and ramipril 5 mg during 6 days, the AUC of ramipril was increased by 21% while the C_{max} was decreased by 63%. The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2.5 hours.

Based on these results, no dose adjustment for ramipril is required when co administered with Soliqua SoloStar.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No animal fertility studies have been performed with insulin glargine and lixisenatide in combination.

Insulin glargine

In a combined fertility, prenatal and postnatal study in male and female rats at subcutaneous doses up to 10 IU/kg/day (approximately 5 times anticipated clinical exposure based on BSA), insulin glargine was maternotoxic due to dose-dependent hypoglycaemia leading to death at the highest dose. There were no effects of treatment on fertility. Similar effects were seen with NPH insulin.

Lixisenatide

Hypospermatogenesis and focal sperm stasis were observed in dogs treated subcutaneously with lixisenatide. However, this occurred only at high doses (yielding ≥64 times the plasma AUC in patients at the maximum recommended human dose) and dogs were seen to be more sensitive to such toxicity by lixisenatide compared with other species. No related effect on spermatogenesis was seen in healthy men.

Use in pregnancy (Category B3)

Soliqua SoloStar is not recommended in women of childbearing potential not using contraception.

There are no randomised controlled clinical studies on the use of Soliqua SoloStar, insulin glargine, or lixisenatide in pregnant women. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Soliqua SoloStar should be discontinued.

No animal studies have been conducted with the combination of insulin glargine and lixisenatide to evaluate embryofetal toxicity.

Insulin glargine

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) with insulin glargine indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine.

Embryofetal development studies in rats and rabbits have been performed at subcutaneous doses up to 20 IU/kg/day and 2 IU/kg/day, respectively (approximately 10 times and twice anticipated clinical exposure, respectively, based on BSA). The effects of insulin glargine generally did not differ from those observed with NPH insulin in rats or rabbits. However, in rabbits dosed with 2 IU/kg/day there was an increased incidence of dilatation of the cerebral ventricles.

A meta-analysis of eight observational clinical studies including 331 women using Lantus and 371 women using insulin NPH was performed to assess the safety of insulin glargine and insulin NPH in gestational or pregestational diabetes. No significant differences in safety-related maternal or neonatal outcomes were seen between insulin glargine and insulin NPH during pregnancy.

Lixisenatide

Studies in animals have shown reproductive toxicity.

Fetal growth retardation, skeletal abnormalities and delayed ossification occurred in rats treated during gestation to maternally toxic doses resulting in exposures ≥0.5-fold the mean exposure at the maximum recommended human dose (MRHD). In rabbits, impaired ossification and increased incidences of sternebrae abnormalities and rib variations were observed at maternally toxic doses (≥50micrograms/kg/day subcutaneously) yielding exposures ≥40-fold the mean exposure at the MRHD.

In the pre-/postnatal toxicity study in rats subcutaneous treatment with lixisenatide during gestation and lactation caused slightly increased pup mortality at 200µg/kg twice daily and decreased growth in male pups, and slightly decreased suckling and minor developmental delay in fur growth at 20 and 200 µg/kg twice daily (occurring in conjunction with maternal toxicity). No functional or behavioural toxicity was observed in the offspring of rats administered lixisenatide at doses up to 200micrograms/kg twice daily.

Use in lactation

It is unknown whether insulin glargine or lixisenatide is excreted in human milk. A study in lactating rats showed very low transfer of lixisenatide and its metabolites into milk. Due to lack of experience, Soliqua SoloStar should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND 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. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The Soliqua SoloStar phase 3 clinical studies included 834 patients treated with Soliqua SoloStar.

The most frequently reported undesirable adverse reactions during treatment with Soliqua SoloStar were hypoglycaemia and gastrointestinal adverse reactions.

Tabulated list of adverse reactions

The following adverse reactions observed from Soliqua SoloStar clinical investigation are listed below by system organ class and in order of decreasing incidence:

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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 - Adverse reactions observed from Soliqua SoloStar Clinical investigations

System Organ Class	Frequency of occurrence			
	Very common	**Common**	**Uncommon**	**Unknown**
Infections and Infestations			Nasopharyngitis Upper respiratory tract infection	
Immune system disorders			Urticaria	
Metabolism and nutrition disorders	Hypoglycaemia			

System Organ Class	Frequency of occurrence			
Nervous system disorders		Dizziness	Headache	
Gastrointestinal disorders		Nausea Diarrhoea Vomiting	Dyspepsia Abdominal pain	
General disorders and administration site conditions			Fatigue Injection site reactions	
Skin and subcutaneous tissue disorders				Cutaneous* amyloidosis*

*Adverse reaction observed for insulin glargine

Hypoglycaemia

Severe hypoglycaemic 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. (see section 4.4 SPECIAL WARNINGS AND PRECAUSIONS FOR USE).

The following table describes the rate of documented symptomatic hypoglycaemia (≤ 3.9mmol/L) and severe hypoglycaemia for both Soliqua SoloStar and comparator.

Table 3 - Documented symptomatic or severe hypoglycaemic adverse reactions

	Insulin Naïve Patients			**Switch from basal insulin**	
	Soliqua SoloStar	**Insulin glargine (U100)**	**Lixisenatide**	**Soliqua SoloStar**	**Insulin glargine (U100)**
N	469	467	233	365	365
Documented symptomatic hypoglycaemia*					
Patients with event, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)	146 (40.0)	155 (42.5)
Events per patient-year, n	1.44	1.22	0.34	3.03	4.22
Severe hypoglycaemia**					
Events per patient- year, n	0	<0.01	0	0.02	<0.01

	Insulin Naïve Patients	Switch from basal insulin

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

Gastrointestinal disorders
Gastrointestinal adverse reactions (nausea, vomiting and diarrhea) were frequently reported adverse reactions during the treatment period. In patients treated with Soliqua SoloStar, the incidence of related nausea, diarrhoea and vomiting was 8.4%, 2.2% and 2.2%, respectively. Gastrointestinal adverse reactions were mostly mild and transient in nature. In patients treated with lixisenatide, the incidence of related nausea, diarrhoea and vomiting was 22.3%, 3% and 3.9%, respectively.

Skin and subcutaneous tissue disorders

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

Localised cutaneous amyloidosis at the injection site has occurred with insulins. Hyperglycaemia has been reported with repeated insulin injections into areas of cutaneous amyloidosis; hypoglycaemia has been reported with a sudden change to an unaffected injection site.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. (see section 4.4 Special warnings and precautions for use).

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

Immune system disorders
Allergic reactions (urticaria) possibly related with Soliqua SoloStar 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
As with all therapeutic proteins, administration of Soliqua SoloStar may cause formation of antibodies against insulin glargine and/or lixisenatide.
After 30 weeks of treatment with Soliqua SoloStar in two phase 3 trials, the incidence of formation of anti-insulin glargine antibodies was 21.0% and 26.2%. In approximately 93% of the patients, anti-insulin glargine antibodies showed cross-reactivity to human insulin. The incidence

of formation of anti-lixisenatide antibodies was approximately 43%. Neither status for anti-insulin glargine antibodies nor for anti-lixisenatide antibodies had a clinically relevant impact on safety or efficacy.

Injection Site reactions
Some patients (1.7%) taking insulin containing therapy, including Soliqua SoloStar have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting

4.9 OVERDOSE

Limited clinical data are available with regard to overdose of Soliqua SoloStar.

Hypoglycaemia and gastrointestinal adverse reactions may develop if a patient is dosed with more Soliqua SoloStar than required.

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

ATC Code: A10AE54

Mechanism of action

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

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

Lixisenatide 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.

Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved. Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose is absorbed and appears in the circulation.

Pharmacodynamic effects

The combination of insulin glargine and lixisenatide has no impact on the pharmacodynamics of insulin glargine. The impact of the combination of insulin glargine and lixisenatide on the pharmacodynamics of lixisenatide has not been studied in phase 1 studies.

Consistent with a relatively constant concentration/time profile of insulin glargine over 24 hours with no pronounced peak when administered alone, the glucose utilisation rate/time profile was similar, no pronounced peak, when given in the combination insulin glargine/lixisenatide.

The time course of action of insulins, including Soliqua SoloStar may vary between individuals and within the same individual.

Insulin glargine

In clinical studies with insulin glargine (100 units/mL) the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin.

Lixisenatide

In a 28-day placebo controlled study in patients with type 2 diabetes assessing the effects of 5 to 20 micrograms lixisenatide once-daily or twice-daily doses on blood glucose induced by a standardised breakfast test meal, 10 and 20 micrograms once daily or twice daily lixisenatide improved glycaemic control through the effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes. Lixisenatide administered in this study in the morning at a dose of 20 micrograms once daily maintained statistically significant decreases in postprandial blood glucose after breakfast, lunch and dinner.

Postprandial glucose

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

Insulin secretion

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

Gastric emptying

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

Glucagon secretion

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

Cardiac electrophysiology (QTc)

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

Heart Rate

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

Clinical trials

Overview of Clinical Studies

The safety and effectiveness of Soliqua SoloStar on glycaemic control were evaluated in two randomised clinical studies in patients with type 2 diabetes mellitus:

- Add onto metformin [Insulin Naïve][Study EFC 12404 LixiLan-O]
- Switch from basal insulin [Study EFC 12405 LixiLan-L]

In each of the active controlled trials, treatment with Soliqua SoloStar produced clinically and statistically significant improvements in hemoglobin A1c (HbA1c). Reaching lower HbA1c levels and achieving greater HbA1c reduction did not increase rates of hypoglycaemia with combination treatment versus insulin glargine alone [see section 4.8 ADVERSE EFFECTS]

In the Add-on to metformin clinical study [LixiLan-O] the starting dose was 10 units of insulin glargine and 5micrograms lixisenatide. In the switch from basal insulin clinical study the starting dose was 20 units of insulin glargine and 10 micrograms lixisenatide or 30 units of insulin glargine and 10 micrograms lixisenatide depending on the previous insulin dose. In both studies the dose was titrated once weekly, based on median fasting self-measured plasma glucose values.

Clinical Study in Patients with Type 2 Diabetes Uncontrolled on OAD treatment

Add-on to Metformin [Insulin Naïve]

A total of 1170 patients with type 2 diabetes were randomised in an open label, 30-week, active-controlled study to evaluate the efficacy and safety of Soliqua SoloStar compared to the individual components, insulin glargine (100 units/mL) and lixisenatide (20micrograms).

Patients with type 2 diabetes, treated with metformin alone or metformin and a second OAD treatment that could be a sulfonylurea or a glinide or a sodium-glucose co transporter-2 (SGLT-2) inhibitor or a dipeptidyl peptidase-4 (DPP-4) inhibitor, and who were not adequately controlled with this treatment (HbA1c range 7.5% to10% for patients previously treated with metformin alone and 7.0% to 9 % for patients previously treated with metformin and a second oral anti-diabetic treatment) entered a run-in period for 4 weeks. During this run-in phase metformin treatment was optimised and any other OADs were discontinued. At the end of the run-in period, patients who remained inadequately controlled (HbA1c between 7% and 10%) were randomised to either Soliqua SoloStar, insulin glargine or lixisenatide. Of the 1479 patients who started the run-in phase, 1170 were randomised. The main reasons for not entering the randomised phase were FPG value > 13.9 mmol/L and HBA1c value <7% or >10% at end of the run-in phase.

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

At Week 30, Soliqua SoloStar provided statistically significant improvement in HbA1c (p-value <0.0001) compared to the individual components. In a pre-specified analysis of this primary endpoint, the differences observed were consistent with regard to baseline HbA1c (<8% or >=8%) or baseline OAD use (metformin alone or metformin plus second OAD).

See Table 4 and Figure 1 for the other end points in the study.

Table 4 - Results at 30 weeks - Add-on to metformin clinical study (mITT population)

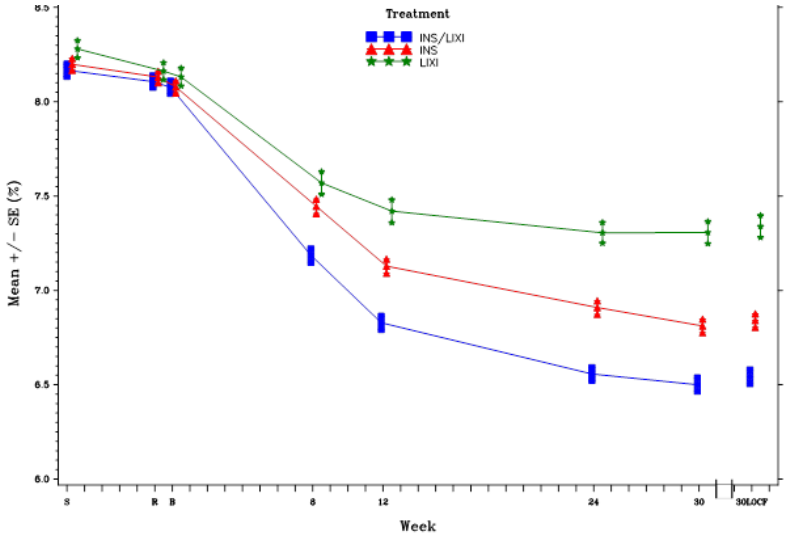
	Soliqua SoloStar	Insulin glargine (U100)	Lixisenatide
Number of subjects (mITT)	468	466	233
HbA1c (%)			
Baseline (mean; post run-in phase)	8.1	8.1	8.1
End of study (mean)	6.5	6.8	7.3
LS change from baseline (mean)	-1.6	-1.3	-0.9
Difference vs. insulin glargine [95% confidence interval] (p-value)	-0.3 [-0.4, -0.2] (<0.0001)		
Difference vs. lixisenatide [95% confidence interval] (p-value)			-0.8 [-0.9, -0.7] (<0.0001)
Number of Patients (%) reaching HbA1c <7% at week 30*	345 (74%)	277 (59%)	77 (33%)
Fasting Plasma glucose (mmol/L)			
Baseline (mean)	9.88	9.75	9.79
End of study (mean)	6.32	6.53	8.27
LS change from baseline (mean)	-3.46	-3.27	-1.50
LS difference versus glargine (mean) [95%CI] (p-value)		-0.19 [-0.420 to 0.038] (0.1017)	
LS difference versus lixisenatide (mean) [95%CI] (p-value)			-1.96 [-2.246 to -1.682] (<0.0001)
2 hour PPG (mmol/L)**			

	Soliqua SoloStar	Insulin glargine (U100)	Lixisenatide
Baseline (mean)	15.19	14.61	14.72
End of study (mean)	9.15	11.35	9.99
LS change from baseline	-5.68 [-2.31]	-3.31 [-0.18]	-4.58 [-3.23]
LS difference versus glargine (mean)[95%CL]		-2.38 (-2.79 to -1.96)	
LS difference versus lixisentide (mean) [95%CL]			-1.10 (-1.63 to -0.57)
Mean body weight (kg)			
Baseline (mean)	89.4	89.8	90.8
LS change from baseline (mean)	-0.3	1.1	-2.3
Comparison versus insulin glargine [95% confidence interval] (p-value)		-1.4 [-1.9 to -0.9] (<0.0001)	
Comparison versus lixisenatide [95% confidence interval] *			2.01 [1.4 to 2.6]
Insulin glargine daily dose			
LS insulin dose at week 30 (mean)	39.8	40.5	NA

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

**2hr PPG minus the pre-meal glucose value

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



*LOCF = Last observation carried forward.

Clinical Studies in Patients with Type 2 Diabetes Uncontrolled on Basal Insulin

Switch from Basal Insulin

A total of 736 patients with type 2 diabetes participated in a randomised, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study to evaluate the efficacy and safety of Soliqua SoloStar compared to insulin glargine (100 units/mL).

Patients screened had type 2 diabetes, were treated with basal insulin for at least 6 months, receiving a stable daily dose of between 15 and 40 units alone or combined with 1 or 2 OADs (metformin or a sulfonylurea or a glinide or a SGLT-2 inhibitor or a DPP-4 inhibitor), had an HbA1c between 7.5% and 10% and a FPG less than or equal to 9.99 mmol/L or 11.1 mmol/L depending on their previous anti-diabetic treatment.

After screening, eligible patients (n=1018) entered a 6-week run-in phase where patients remained on or were switched to insulin glargine, in case they took another basal insulin, and had their insulin dose titrated/stabilised while continuing metformin (if previously taken. Any other OADs were discontinued.

At the end of the run-in period, patients with an HbA1c between 7 and 10% , mean SMPG $\leq$ 7.77 mmol/L and insulin glargine daily dose of 20 to 50 units, were randomised to either Soliqua SoloStar (n=367) or insulin glargine (n=369).

This type 2 diabetes population had the following characteristics: Mean age was 60 years with the majority (56.3%) being aged of 50 to 64 years, and 53.3 % were female. The mean BMI at baseline was 31.1 kg/m2 with 57.3% of patients having a BMI $\geq$30 kg/m2. The mean diabetes

duration was approximately 12 years and the mean duration of previous basal insulin treatment was approximately 3 years. At screening 64.4% of patients were receiving insulin glargine as basal insulin and 95.0% received at least 1 concomitant OAD. 10.6% of patients were not taking any metformin at screening.

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

See Table 5 and Figure 2 for other end points in the study.

Table 5 - Results at 30 weeks -Study Type 2 Diabetes Uncontrolled on Basal Insulin mITT population

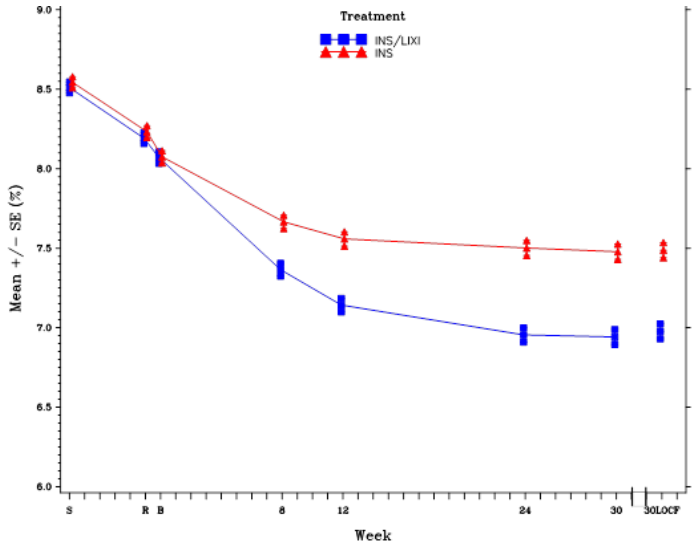
	Soliqua SoloStar	Insulin glargine (U100)
Number of subjects (mITT)	366	365
HbA1c (%)		
At screening (mean)	8.5	8.5
Baseline (mean; post run-in phase)	8.1	8.1
End of treatment (mean)	6.9	7.5
LS change from baseline (mean)	-1.1	-0.6
Difference versus insulin glargine [95% confidence interval] (p-value)	-0.5 [-0.6, -0.4] (<0.0001)	
Patients [n (%)] reaching HbA1c <7% at week 30 *	201 (54.9%)	108 (29.6%)
Fasting Plasma glucose (mmol/L)		
Baseline (mean)	7.33	7.32
End of study (mean)	6.78	6.69
LS change from baseline (mean)	-0.35	-0.47
Difference versus insulin glargine [95% confidence interval]	0.11 [-0.21 to 0.43]	
2 hour PPG (mmol/L)**		
Baseline (mean)	14.85	14.97
End of Study (mean)	9.91	13.41
LS change from baseline to week 30 (mean)	-4.72 [-3.90]	-1.39 [-0.47]
LS difference versus glargine (mean) [95%CI]	-3.33 (-3.89 to -2.77)	
Mean body weight (kg)		
Baseline (mean)	87.8	87.1

	Soliqua SoloStar	Insulin glargine (U100)
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)	
Insulin glargine daily dose		
Baseline (mean)	35.0	35.2
Endpoint (mean)	46.7	46.7
LS insulin dose change at week 30 (mean)	10.6	10.9

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

**2 hour PPG minus the pre-meal glucose value

Figure 2 - Mean HbA1c (%) at start of screening, at randomisation, 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 SoloStar.

Insulin glargine

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomised, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The 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. (Refer to Lantus PI for more information).

Lixisenatide

The ELIXA study was a randomised, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients (n=6068) with type 2 diabetes mellitus after a recent Acute Coronary Syndrome. The primary composite efficacy endpoint was the time to the first occurrence of any of the following events positively adjudicated by the Cardiovascular Events Adjudication Committee: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. CV secondary endpoints included a composite of the primary endpoint, or hospitalisation for heart failure or coronary revascularization. Changes in urinary albumin/creatinine ration (UACR) at 108 weeks were also a pre-specified secondary endpoint.

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

The incidence of the primary endpoint was similar in the lixisenatide and placebo groups: the hazard ratio (HR) for lixisenatide versus placebo was 1.017, with an associated 2-sided 95% confidence interval (CI) of 0.886 to 1.168. Similar percentages between treatments were also observed for the secondary endpoints, and for all the individual components of the composite endpoints. The percentages of patients hospitalised for heart failure were 4.0% and 4.2% in the lixisenatide and placebo group, respectively (HR [95% CI] = 0.96 [0.75 – 1.23]).

A smaller increase in UACR from baseline to Week 108 was observed in lixisenatide compared to placebo: -10.04% ± 3.53%; 95% CI = -16.95%, -3.13%. (refer to the Lyxumia PI for more information).

5.2 PHARMACOKINETIC PROPERTIES

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

Compared to administration of lixisenatide alone, the C_{max} is lower whereas the AUC is generally comparable when administered as Soliqua SoloStar. The observed differences in the PK of lixisenatide when given as Soliqua SoloStar 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 following administration of insulin glargine/lixisenatide combination was 86-88% compared to administration of separate simultaneous injections of insulin glargine and lixisenatide. The difference is not considered clinically relevant.

After subcutaneous administration of insulin glargine/lixisenatide combinations to patients with type 1 diabetes, the median t_{max} of lixisenatide was in the range of 2.5 to 3.0 hours. AUC was comparable while there was a small decrease in C_{max} of lixisenatide of 22-34% compared with separate simultaneous administration of insulin glargine and lixisenatide, which is not likely to be clinically significant.

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

Distribution

Lixisenatide

Lixisenatide has a moderate level of binding (55%) to human proteins. The apparent volume of distribution of lixisenatide after subcutaneous administration of insulin glargine/lixisenatide combinations (Vz/F) is approximately 100 L.

Insulin glargine

The apparent volume of distribution of insulin glargine after subcutaneous administration of the insulin glargine/lixisenatide combinations (Vss/F) is approximately 1700 L.

Metabolism

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 drug and these degradation products are also present in the circulation.

Lixisenatide

Lixisenatide was found to be extensively metabolised by human kidney and liver S9 fractions *in vitro*. 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.

Excretion

Insulin glargine

Insulin glargine is degraded to metabolites M1 and M2 independent of its concentration in the formulation.

Lixisenatide

After multiple dose administration in patients with type 2 diabetes, mean apparent half-life generally ranged from 1.5 to 4.5 hours and the mean apparent clearance ranged from 20 to 67 L/h at steady state.

Special Populations

Gender, Race and age

Insulin glargine

Effect on 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 analysis based on race and gender did not show difference in safety and efficacy.

Lixisenatide

Age had no clinically relevant effect on the pharmacokinetics of lixisenatide based on a population pharmacokinetic data analysis in patients with type 2 diabetes. In a pharmacokinetic study in elderly non diabetic subjects, administration of lixisenatide 20 micrograms resulted in a mean increase of lixisenatide AUC by 29 % in the elderly population (11 subjects between 65 and 74 years and 7 subjects aged ≥75 years) compared to 18 subjects aged 18 to 45 years, likely related to reduced renal function in the older age group.

Ethnic origin had no clinically relevant effect on the pharmacokinetics of lixisenatide based on the results of pharmacokinetic studies in Caucasian, Japanese and Chinese subjects.

Gender has no clinical relevant effect on the Pharmacokinetics of lixisenatide.

Paediatric Patients

Safety and effectiveness of Soliqua SoloStar has not been established in paediatric patients.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Soliqua SoloStar 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 SoloStar in patients with hepatic impairment.

Renal Impairment

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

Compared to healthy subjects (N=4; CrCl greater than or equal to 90 mL/min), plasma C_{max} 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, respectively, (CrCl 60-89, 30-59 and 15-29 mL/min, respectively); plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively.

Insulin glargine has not been studied in patients with renal impairment. In patients with renal impairment, however insulin requirements may be diminished due to reduced insulin metabolism.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Insulin glargine

Insulin glargine was negative in tests for mutagenicity in bacterial and mammalian cells and for clastogenicity (*in vitro* in V79 cells and *in vivo* in Chinese hamsters)

Lixisenatide

Lixisenatide had no genotoxic effects, based on one *in vivo* micronucleus test in mice (involving IV administration up to 5000 micrograms/kg) and *in vitro* tests: the modified Ames test with or without metabolic activation, and *in vitro* mammalian chromosome aberration test in cultured human lymphocytes.

Carcinogenicity

No carcinogenicity studies have been performed with insulin glargine and lixisenatide in combination.

Insulin glargine

Two year carcinogenicity studies were performed in mice and rats at subcutaneous doses up to 12.5 IU/kg/day (approximately 3 and 7 times anticipated clinical exposure based on BSA). Malignant fibrous histiocytomas were found at insulin glargine injection sites in male rats and mice. The incidence of these tumours was not dose-dependent and tumours were also present at acid vehicle control injection sites but not at saline control injection sites or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Other insulin preparations are known to cause an increase in mammary tumours in female rats. No such increase in tumours was seen with insulin glargine probably because of the lower doses of insulin glargine used in the mouse and rat carcinogenicity studies.

Lixisenatide

Lixisenatide caused thyroid C-cell tumours in 2-year subcutaneous carcinogenicity studies in rodents. In mice, thyroid C-cell adenoma (together with focal C-cell hyperplasia) was increased at ≥400 micrograms/kg/day, yielding systemic exposure levels ≥29-fold greater than in humans at the maximum recommended human dose. No treatment-related increase in tumour incidence was seen in mice at 80 micrograms/kg/day (relative exposure, 7). In rats, focal C-cell hyperplasia and C-cell adenoma were increased at all dose levels tested (≥80 micrograms/kg/day: yielding exposure ratios ≥9), and C-cell carcinoma was observed at ≥400 micrograms/kg/day (yielding ≥35-times the human exposure). These findings are considered to be caused by a GLP-l receptor-mediated mechanism to which rodents are particularly sensitive. Human relevance cannot presently be completely excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glycerol
Methionine
Metacresol (preservative)
Zinc chloride
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Unopened/not in use pre-filled pen: 2 years

Shelf-life after first use of the pen: 28 days

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened/not in use pre-filled pen

Soliqua SoloStar must be stored between +2°C and +8 °C (in a refrigerator) and protected from light. Do not allow the insulin to freeze, discard if frozen. Discard after expiration date.

Do not put Soliqua SoloStar next to the freezer compartment or a freezer pack.

Opened/in-use pre-filled pen:

Do not allow the insulin to freeze, discard if frozen.

Opened pre-filled pen must be discarded after 28 days (4 weeks) from the first use. The open pre-filled pen of Soliqua SoloStar should be kept away from direct heat and light, at room temperature (below 25°C).

These storage conditions are summarized in the following table:

	Not in-use (unopened) Refrigerated (2°C - 8°C).	**In-use (opened) Room temperature (below 25°C).**
Pre-filled pen	Until expiration date	28 days (4 weeks) **(Do not refrigerate)**

6.5 NATURE AND CONTENTS OF CONTAINER

Soliqua SoloStar is available in two SoloStar pre-filled pen as below. The 3 mL cartridge is sealed in a disposable pen injector.

3mL solution in a cartridge (type I colourless glass) with a black plunger (bromobutyl rubber) and a flanged cap (aluminum) with inserted laminated sealing disks (bromobutyl rubber on the product side and polyisoprene on the outside).

Needles are not included in the pack.

Dosage Unit/Strength	**Package size**
10 to 40 prefilled pen 100 units/mL insulin glargine 50 micrograms/mL lixisenatide	Pack sizes 1,3 and 5*
30 to 60 disposable prefilled pen 100 units/mL insulin glargine 33 micrograms/mL lixisenatide	Pack sizes 1,3 and 5 *

*Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie
Auckland
New Zealand
Toll Free Number (medical information): 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

11 July 2019

10 DATE OF REVISION

16 November 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Spelling corrections
4.2	Minor updates to the method of administration
4.4	Addition of precaution/warning
4.8	Addition of t subcutaneous tissues disorders