HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOLIQUA 100/33 safely and effectively. See full prescribing information for SOLIQUA 100/33.

SOLIQUA® 100/33 (insulin glargine and lixisenatide injection), for subcutaneous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

SOLIQUA 100/33 is a combination of a long-acting human insulin analog with a glucagon-like peptide-1 (GLP-1) receptor agonist 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) or lixisenatide. (1)

Limitations of Use (1):

- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not recommended for use in combination with any other product containing lixisenatide or another GLP-1 receptor agonist.
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Not recommended for use in patients with gastroparesis.
- Has not been studied in combination with prandial insulin.

----------DOSAGE AND ADMINISTRATION----------

- Discontinue therapy with lixisenatide or basal insulin prior to initiation of SOLIQUA 100/33. (2.1)
- In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily. (2.1)
- In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily. (2.1)
- Inject once a day within the hour prior to the first meal of the day. (2.1)
- Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). (2.1)
- SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. (2.1, 2.2)
- Use alternative antidiabetic products if patients require a SOLIQUA 100/33 daily dosage below 15 units or over 60 units (2.1)
- See Full Prescribing Information for titration recommendations. (2.2)
- Inject subcutaneously in thigh, upper arm, or abdomen. (2.4)
- Do not administer intravenously, intramuscularly, or by an infusion pump. (2.4)
- Do not dilute or mix with any other insulin products or solutions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 units of insulin glargine per mL and 33 mcg of lixisenatide per mL in a 3 mL single-patient use pen. (3)

----------CONTRAINDICATIONS----------

- During episodes of hypoglycemia (4)
- Hypersensitivity to SOLIQUA 100/33 either of the active drug substances (insulin glargine or lixisenatide), or any of its excipients. Hypersensitivity reactions including anaphylaxis have occurred with both lixisenatide and insulin glargine (4)

----------WARNINGS AND PRECAUTIONS----------

- *Anaphylaxis and serious hypersensitivity reactions*: Severe, life-threatening, and generalized allergic reactions can occur. Instruct patients to discontinue if a reaction occurs and promptly seek medical attention. (5.1)
- *Pancreatitis*: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. (5.2)
- *Never share* a SOLIQUA 100/33 prefilled pen between patients, even if the needle is changed. (5.3)
- *Hyperglycemia or hypoglycemia with changes in SOLIQUA 100/33 regimen:* Carry out under close medical supervision. (5.4)
- *Overdose due to Medication errors*: SOLIQUA 100/33 contains two drugs. Instruct patients to always check the label before each injection since accidental mix-ups with insulin-containing products can occur. Do not exceed the maximum dose or use with other GLP-1 receptor agonists. (5.5)
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, coadministered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. (5.6)
- *Acute Kidney Injury*: Monitor renal function in patients with renal impairment and in patients with severe GI adverse reactions. Use is not recommended in patients with end-stage renal disease (5.7)
- *Immunogenicity*: Patients may develop antibodies to insulin glargine and lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection-site reactions or allergic reactions, alternative antidiabetic therapy should be considered. (5.8)
- *Hypokalemia*: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.9)
- *Fluid retention and heart failure with use of thiazolidinediones (TZDs)*: Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.10)
- *Macrovascular Outcomes*: Clinical studies have not shown macrovascular risk reduction with SOLIQUA 100/33. (5.11)

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥ 5% of patients treated with SOLIQUA 100/33 include hypoglycemia, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Drugs that affect glucose metabolism:* Adjustment of SOLIQUA 100/33 dosage may be needed; closely monitor blood glucose. (7.1)
- *Antiadrenergic Drugs* (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Hypoglycemia signs and symptoms may be reduced. (7.1)
- *Effects of delayed gastric emptying on oral medications:* Lixisenatide delays gastric emptying which may impact absorption of concomitantly administered oral medications. Oral contraceptives and other medications such as antibiotics and acetaminophen should be taken at least 1 hour prior to SOLIQUA 100/33 administration or 11 hours after. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy*: SOLIQUA 100/33 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

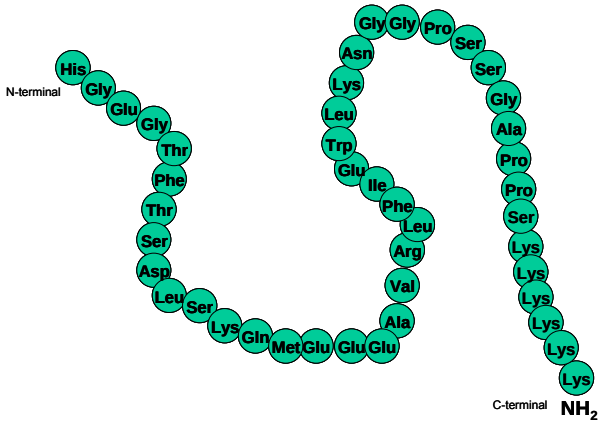
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

Lixisenatide

Lixisenatide is a synthetic analogue of human GLP-1 which acts as a GLP-1 receptor agonist. Lixisenatide is a peptide containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44). The order of the amino acids is given in the figure below. Its molecular weight is 4858.5, and the empirical formula is $C_{215}H_{347}N_{61}O_{65}S$ with the following chemical structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SOLIQUA 100/33

SOLIQUA 100/33 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 and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

Lixisenatide

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

12.2 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, lixisenatide reduced fasting plasma glucose and postprandial blood glucose $AUC_{0\text{-}300min}$ compared to placebo (-33.8 mg/dL and -387 mg•h/dL, 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.

Treatment with lixisenatide 20 mcg 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.

Cardiac electrophysiology (QTc)

At a dose 1.5-times the recommended dose, lixisenatide does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

SOLIQUA 100/33

The insulin glargine/lixisenatide ratio has no relevant impact on the PK of insulin glargine in SOLIQUA 100/33.

Compared to administration of lixisenatide alone, the C_{max} is lower whereas the AUC is generally comparable when administered as SOLIQUA 100/33. The insulin glargine/lixisenatide ratio has no impact on the PK of lixisenatide in SOLIQUA 100/33. The observed differences in the PK of lixisenatide when given as SOLIQUA 100/33 or alone are not considered to be clinically relevant.

Absorption

After subcutaneous administration of insulin glargine/lixisenatide combinations, insulin glargine showed no pronounced peak. Exposure to insulin glargine ranged from 86% to 101% compared to administration of insulin glargine alone.

After subcutaneous administration of insulin glargine/lixisenatide combinations, the median t_{max} of lixisenatide was in the range of 2.5 to 3.0 hours. There was a small decrease in C_{max} of lixisenatide of 22-34% compared with separate simultaneous administration of insulin glargine and lixisenatide, which is not likely to be clinically significant. There are no clinically relevant differences in the rate of absorption when lixisenatide is administered subcutaneously in the abdomen, thigh, or arm.

Distribution

The protein binding of lixisenatide is 55%.

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 (21^{A}-Gly-insulin) and M2 (21^{A}-Gly-des-30^{B}-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Lixisenatide is presumed to be eliminated through glomerular filtration, and proteolytic degradation.

After multiple dose administration 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

Effects of age, body weight, gender and race

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: Age, body weight, gender, and race were not observed to meaningfully affect the pharmacokinetics of lixisenatide in population PK analyses.

Renal impairment

Lixisenatide: Compared to healthy subjects (N=4), plasma C_{max} of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild (CLcr 60-89 mL/min [N=9]), moderate (CLcr 30-59 mL/min [N=11]), and severe (CLcr 15-29 mL/min [N=8]) renal impairment. Plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively *[see Use in Specific Populations (8.6)]*.

Drug interaction studies with SOLIQUA 100/33

Due to their peptidic nature, insulin glargine and lixisenatide have no relevant potential to induce or inhibit CYP isozymes and therefore, no direct drug interaction is expected.

Beyond the interaction studies performed with the individual components no additional interaction studies were conducted with SOLIQUA 100/33.

Drug interaction studies with lixisenatide

The drug interaction studies focused on the potential for lixisenatide to influence the rate and extent of exposure to coadministered drugs due to its known delaying effect on gastric emptying.

Acetaminophen

Lixisenatide 10 mcg did not change the overall exposure (AUC) of acetaminophen following administration of a single dose of acetaminophen 1000 mg, whether before or after lixisenatide. No effects on acetaminophen C_{max} and t_{max} were observed when acetaminophen was administered 1 hour before lixisenatide. When administered 1 or 4 hours after 10 mcg lixisenatide, C_{max} of acetaminophen was decreased by 29% and 31%, respectively, and median t_{max} was delayed by 2.0 and 1.75 hours, respectively.

Oral contraceptives

Administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after 10 mcg lixisenatide, did not change C_{max}, AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel.

Administration of the oral contraceptive 1 hour or 4 hours after lixisenatide did not affect the overall exposure (AUC) and mean terminal half-life ($t_{1/2}$) of ethinylestradiol and levonorgestrel. However, 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.

Atorvastatin

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

Warfarin and other coumarin derivatives

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

Digoxin

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

Ramipril

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SOLIQUA 100/33

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

Insulin glargine

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 2-times and for the mouse approximately 1-times the recommended human subcutaneous high dose of 60 Units/day (0.0364 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. 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.

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).

In a combined fertility and prenatal and postnatal study with insulin glargine in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately 2-times the recommended human subcutaneous maximum dose of 60 Units/day (0.0364 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.

Lixisenatide

Carcinogenicity studies of 2-years durations were conducted in CD-1 mice and Sprague-Dawley rats with twice daily subcutaneous doses of 40, 200, or 1000 mcg/kg. A statistically significant increase in thyroid C-cell adenomas was observed in males at 2,000 mcg/kg/day, resulting in exposures that are >180-times the human exposure achieved at 20 mcg/day based on plasma AUC.

Statistically significant increases in thyroid C-cell adenomas were seen at all doses in rats, resulting in systemic exposures that are ≥15-times the human exposure achieved at 20 mcg/day based on plasma AUC. A numerical increase in thyroid C-cell carcinomas was observed in rats at ≥400 mcg/kg/day, resulting in systemic exposures that are ≥56-times the human exposure achieved at 20 mcg/day based on plasma AUC.

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).

Impairment of fertility

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 400-times the clinical systemic exposure at 20 mcg/day based on mcg/m^2.

14 CLINICAL STUDIES

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 100/33 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 oral antidiabetic drugs (OADs) (metformin, sulfonylurea, glinide, SGLT-2 inhibitor or a DPP-4 inhibitor), had an HbA1c between 7.5% and 10% and a FPG less than or equal to 180 mg/dL or 200 mg/dL depending on their previous antidiabetic treatment.

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. At screening the mean duration of diabetes was approximately 12 years, the mean

BMI was approximately 31 kg/m^2, mean eGFR was 80.6 mL/min/1.73 m² and 86.1% of patients had an eGFR ≥60 mL/min.

After screening, eligible patients (n=1018) entered a 6-week run-in phase where patients remained on or were switched to insulin glargine 100 units/mL, if they were treated with another basal insulin, and had their insulin glargine dose titrated/stabilized while continuing metformin (if previously taken). The mean HbA1c decreased during run-in period from 8.5 to 8.1%. Any other OADs were discontinued.

At the end of the run-in period, patients with an HbA1c between 7 and 10%, FPG ≤140 mg/dL and insulin glargine daily dose of 20 to 50 units (mean of 35 units), were randomized to either SOLIQUA 100/33 (n=367) or insulin glargine 100 units/mL (n=369).

SOLIQUA 100/33 and insulin glargine were to be titrated weekly to target a fasting plasma glucose goal of <100 mg/dL. The mean dose of insulin glargine at baseline was 35 units. The maximum dose of insulin glargine allowed in the trial was 60 units (insulin dose cap) in both groups. The targeted fasting plasma glucose goal was achieved in 33% of patients in both groups at 30 weeks.

At Week 30, there was a reduction in HbA1c from baseline of -1.1% for SOLIQUA 100/33 and –0.6% for insulin glargine (100 units/mL). The mean difference (95% CI) in HbA1c reduction between SOLIQUA 100/33 and insulin glargine was -0.5 [-0.6, -0.4] and statistically significant. The trial was designed to show the contribution of the GLP-1 component to glycemic lowering and the insulin glargine dose 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 100/33 and insulin glargine at week 30 was 46.7 units (for SOLIQUA 100/33: 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. See Table 5 for the other endpoints in the study.

Table 5: Results of a 30-Week Study in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin

	SOLIQUA 100/33	**Insulin Glargine 100 units/mL**
Number of Subjects (randomized and treated)	365	365
HbA1c (%)		
Baseline (mean; post run-in phase)	8.1	8.1
End of study (mean)	6.9	7.5
LS change from baseline (mean)*	-1.1	-0.6
Difference vs insulin glargine [95% confidence interval]	-0.5 [-0.6, -0.4]†	
Patients [n (%)] reaching HbA1c <7% at week 30‡	201 (55.1%)	108 (29.6%)
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	132.3	132.0
End of study (mean)	121.9	120.5
LS change from baseline (mean)	-5.7	-7.0

* Estimated using an ANCOVA with treatment, randomization strata, and country as fixed factors and baseline HbA1c as covariate. 20 (5.5%) patients in the SOLIQUA 100/33 arm and 10 (2.7%) of patients in the insulin glargine 100 units/mL arm had missing HbA1c measurement at Week 30. Missing measurements were imputed using multiple imputation with respective to the baseline value of the subject.

† $p<0.01$; The trial was designed to show the contribution of the GLP-1 component to glucose 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 100/33 and insulin glargine at week 30 was 46.7 units (for SOLIQUA 100/33: 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.

‡ Patients with missing HbA1c measurement at Week 30 were considered as non-responders.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

SOLIQUA 100/33 is an injection supplied as a sterile, clear, colorless to almost colorless solution in a 3 mL prefilled, disposable, single-patient use pen injector:

Dosage Unit/Strength	Package size	NDC #
3 mL SOLIQUA 100/33 disposable prefilled pen 100 units/mL insulin glargine and 33 mcg/mL lixisenatide	Package of 5	0024-5761-05

Needles are not included. Only use needles that are compatible for use with SOLIQUA 100/33 prefilled pen.

16.2 Storage

Prior to first use, SOLIQUA 100/33 pen should be stored in a refrigerator, 36°F-46°F (2°C-8°C). Do not freeze. Protect from light. Discard after the expiration date printed on the label.

SOLIQUA 100/33 should not be stored in the freezer and should not be allowed to freeze. Discard SOLIQUA 100/33 if it has been frozen.

After first use, store at room temperature below 86°F (30°C). Replace the pen cap after each use to protect from light.

Discard pen 14 days after first use.

Always remove the needle after each injection and store the SOLIQUA 100/33 pen without a needle attached. This prevents contamination and/or infection, or leakage of the SOLIQUA 100/33 pen, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, including anaphylaxis, have been reported in clinical trials of SOLIQUA 100/33 and during postmarketing use of other GLP-1 receptor

agonists. If symptoms of hypersensitivity reactions occur, instruct patients to stop taking SOLIQUA 100/33 and seek medical advice promptly *[see Warnings and Precautions (5.1)]*.

Risk of Pancreatitis

Inform patients that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue SOLIQUA 100/33 and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Never Share a SOLIQUA 100/33 Pen

Advise patients that they must never share a SOLIQUA 100/33 prefilled pen with another person, even if the needle is changed because doing so carries a risk for transmission of blood-borne pathogens.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin containing products. Inform patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in SOLIQUA 100/33 regimen can predispose to hyperglycemia or hypoglycemia. Advise patients that changes in SOLIQUA 100/33 regimen should be made under close medical supervision *[see Warnings and Precautions (5.4, 5.6)]*.

Dehydration and Renal Failure

Advise patients treated with SOLIQUA 100/33 of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis *[see Warnings and Precautions (5.7)]*.

Overdose due to Medication Errors

Inform patients that SOLIQUA 100/33 contains two drugs: insulin glargine and lixisenatide. Accidental mix-ups between insulin products have been reported. To avoid medication errors between SOLIQUA 100/33 and other insulin products, instruct patients to always check the label before each injection. Advise patients that the administration of more than 60 units of SOLIQUA 100/33 daily can result in overdose of the lixisenatide component. Instruct patients not to administer concurrently with other glucagon-like peptide-1 receptor agonists.

Administration

Advise patients that SOLIQUA 100/33 must NOT be diluted or mixed with any other insulin or solution and that SOLIQUA 100/33 must only be used if the solution is clear and colorless to almost colorless with no particles visible *[see Dosage and Administration (2.4)]*.

Management of Hypoglycemia and Handling of Special Situations

Instruct patients on self-management procedures including glucose monitoring and management of hypoglycemia and hyperglycemia.

Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals *[see Warnings and Precautions (5.6)]*.

Use in Pregnancy

Advise patients to inform their physicians if they are pregnant or intend to become pregnant *[see Use in Specific Populations (8.1)]*.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Approved: August 2017

INSTRUCTIONS FOR USE
SOLIQUA® 100/33 *(So - lee - kwa)*
(insulin glargine and lixisenatide injection)
for subcutaneous use

Read these instructions carefully before using your SOLIQUA 100/33 pen.

Do not share your SOLIQUA 100/33 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 100/33 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 100/33. Each unit dialed contains 1 unit insulin glargine and 0.33 mcg lixisenatide.

Important information

- Check the label on the SOLIQUA 100/33 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 100/33 in an insulin pump or inject SOLIQUA 100/33 into your vein (intravenously) or muscle (intramuscularly).
- **Do not** mix SOLIQUA 100/33 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

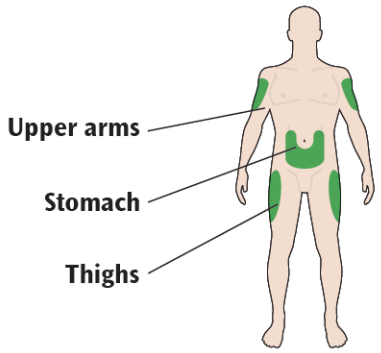
- Talk with your healthcare provider about how to use the SOLIQUA 100/33 pen and how to inject correctly before using your pen.
- Ask for help if you have problems handling the pen, for example if you have vision problems.
- Read all of these instructions before using your pen. You may get too much or 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.soliqua100-33.com** or call sanofi-aventis at **1-800-633-1610**.

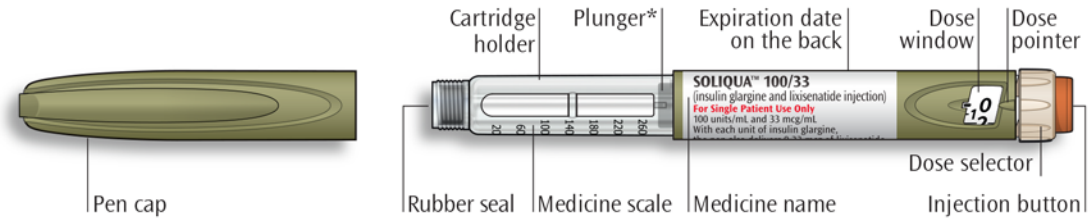
Supplies you will need:

- 1 SOLIQUA 100/33 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 this Instructions for Use)

Places to inject



Get to know your pen



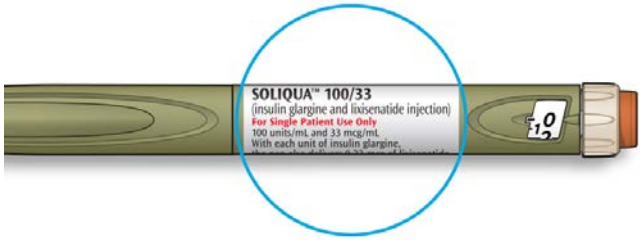
*You will not see the plunger until you have injected a few doses

Step 1: Check your pen

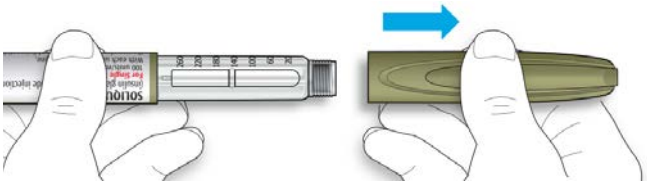
Take a new pen out of the refrigerator at least 1 hour before you inject. Cold medicine is more painful to inject.

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

- Make sure you have the correct medicine. This pen is colored light green with an orange injection button (see the **"Get to know your pen"** diagram).
- **Do not** use your pen after the expiration date on the pen label.

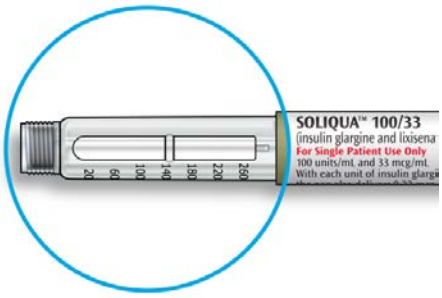


1B Pull off the pen cap.

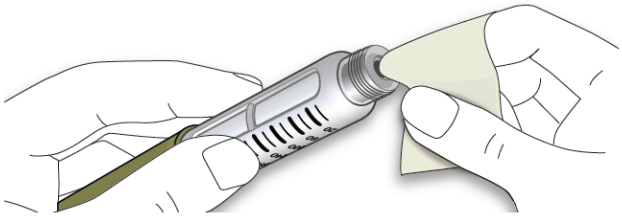


1C Check that the medicine is clear and to almost colorless.

- **If you see small particles, return it to your pharmacy for a replacement.**



1D Wipe the rubber seal with an alcohol swab.



If you have other injector pens

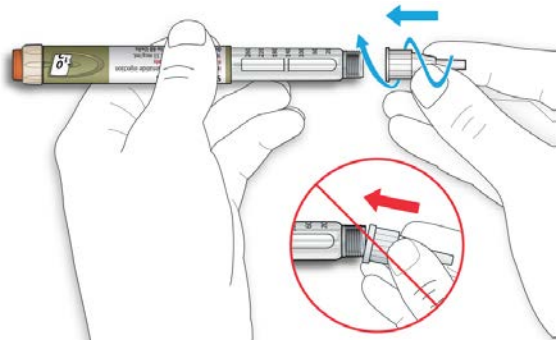
- Making sure you have the correct medicine is especially important if you have other injector pens.

Step 2: Attach a new needle

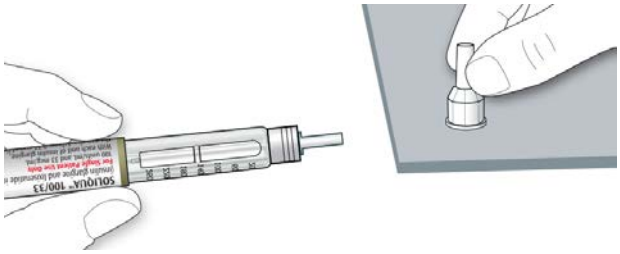
- **Do not** reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection.
- Only use needles that are meant to be used with SOLIQUA 100/33. Needles are supplied separately. If you do not know what needles to use, ask your healthcare provider or pharmacist.

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

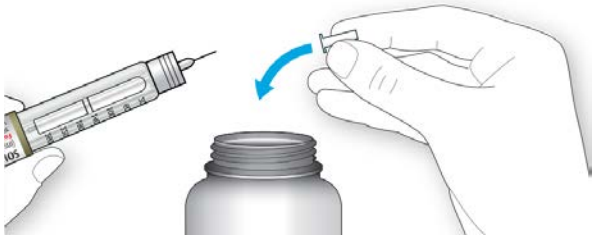
2B Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



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



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



Handling needles

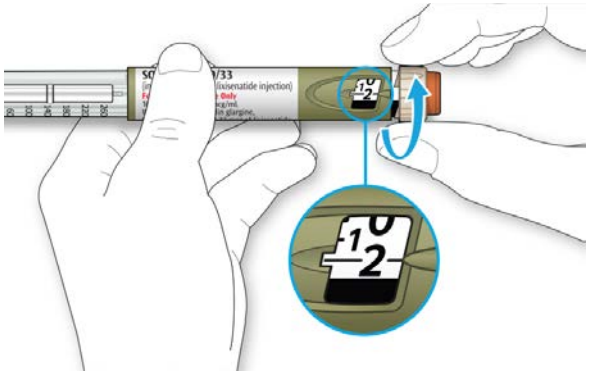
- Take care when handling needles to prevent needle-stick injury and cross-infection.

Step 3: Do a safety test

Perform a safety test before each injection to:

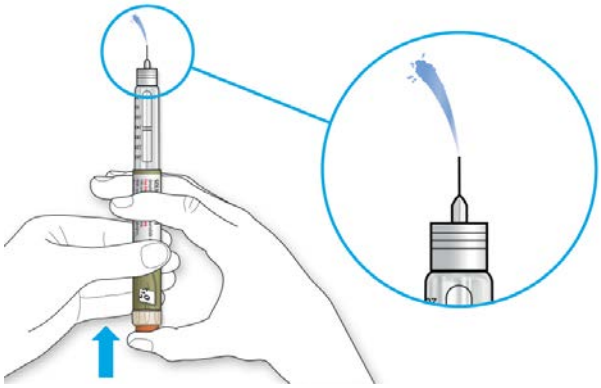
- Check your pen and the needle to make sure they are working properly.
- Make sure that you get the correct dose.

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:

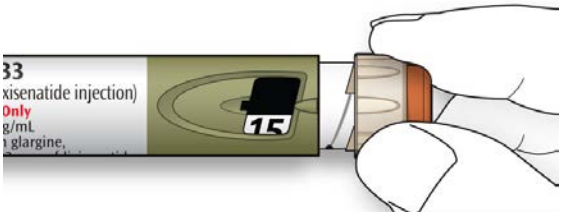
- You may need to repeat this step up to **3** times before seeing the medicine.
- If no medicine comes out after the third time, the needle may be blocked. If this happens:
  - change the needle (**see Step 6** to remove the needle **and Step 2** to attach a new needle),
  - then repeat the safety test (**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, the black area in dose window as shown in the picture.



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 100/33.
- 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 100/33 and it is intended to be used for more than one dose.

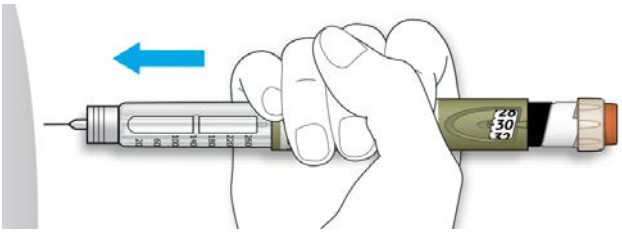
STEP 5: Inject your dose

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.”

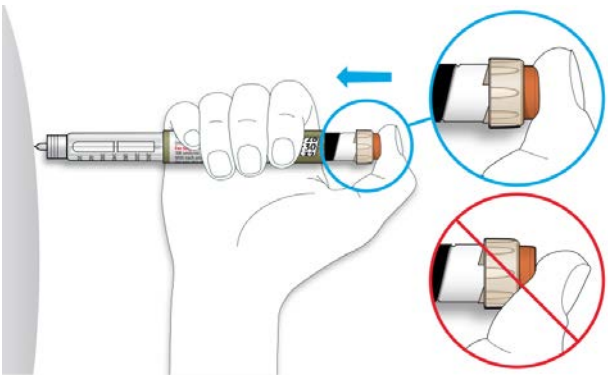
5B Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



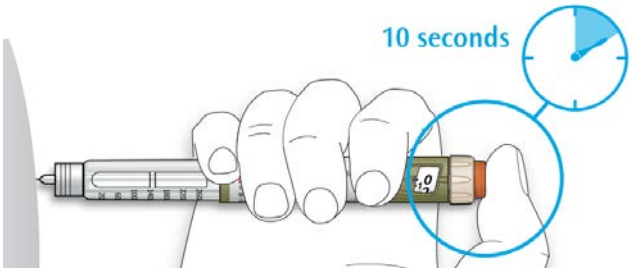
5C Place your thumb on the injection button. Then press all the way in and hold.

- **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:

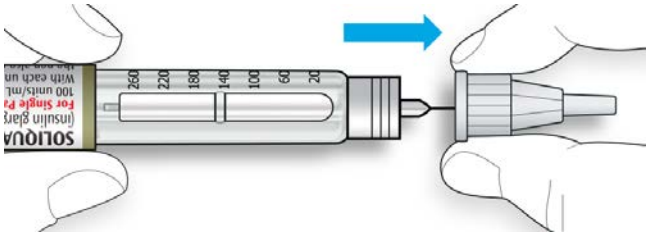
- Change the needle (**see Step 6** to remove the needle **and Step 2** to attach a new needle) then do a safety test (**see Step 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove medicine from your pen.

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.

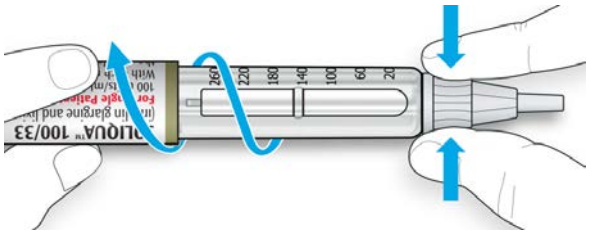
6A **Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.**

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

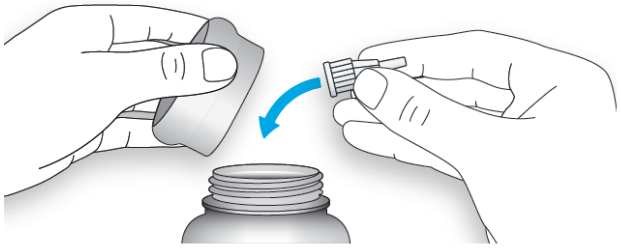


6B **Grip and squeeze the widest part of the outer needle cap.** Turn your pen several times with your other hand to remove the needle.

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

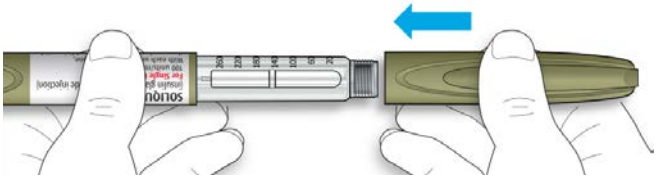


6C **Throw away the used needle in a puncture-resistant container** (see "**Throwing your pen away**" at the end of this Instructions for Use).



6D **Put your pen cap back on.**

- Do not put the pen back in the refrigerator.



Use by

- Only use your pen for up to **14 days** after its first use.

How to store your pen

Before first use
- Keep new pens in the refrigerator between **36°F to 46°F (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, **below 86°F (30°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

- Put the used SOLIQUA 100/33 pen in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the SOLIQUA 100/33 pen in your household trash.
- If you do not have a FDA-cleared sharps disposal 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 labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Approved: August 2017

Medication Guide
SOLIQUA 100/33 (*So - lee - kwa*)
(insulin glargine and lixisenatide injection) for subcutaneous use

What is the most important information I should know about SOLIQUA 100/33?

Do not share your SOLIQUA 100/33 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 100/33 can cause serious side effects including inflammation of the pancreas (pancreatitis), which may be severe and lead to death.

Before using SOLIQUA 100/33, tell your healthcare provider if you have had:

- pancreatitis
- a history of alcoholism
- stones in your gallbladder (cholelithiasis)

These medical problems may make you more likely to get pancreatitis.

Stop taking SOLIQUA 100/33 and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is SOLIQUA 100/33?

SOLIQUA 100/33 is an injectable prescription medicine that contains 2 diabetes medicines, insulin glargine and lixisenatide, that may improve blood sugar (glucose) control in adults with type 2 diabetes when used with diet and exercise in people who are not controlled with long-acting (basal) insulin (less than 60 units daily) or lixisenatide.

- SOLIQUA 100/33 has not been studied in people with a history of pancreatitis.
- SOLIQUA 100/33 is not recommended for people who also take lixisenatide or other medicines called GLP-1 receptor agonists.
- SOLIQUA 100/33 is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- SOLIQUA 100/33 has not been studied in people who have a stomach problem that causes slow emptying of the stomach (gastroparesis). SOLIQUA 100/33 is not for people with slow emptying of the stomach.
- SOLIQUA 100/33 has not been studied in people who also take a short-acting (prandial) insulin.
- **It is not known if SOLIQUA 100/33 is safe and effective in children under 18 years of age.**

Who should not use SOLIQUA 100/33?

Do not use SOLIQUA 100/33 if you:

- are having an episode of low blood sugar (hypoglycemia).
- are allergic to insulin glargine, lixisenatide or any of the other ingredients in SOLIQUA 100/33. See the end of this Medication Guide for a complete list of ingredients in SOLIQUA 100/33.

Symptoms of a severe allergic reaction with SOLIQUA 100/33 may include swelling of your face, lips, tongue, or throat, problems breathing or swallowing, severe rash or itching, fainting or feeling dizzy and very rapid heartbeat.

Before using SOLIQUA 100/33, tell your healthcare provider about all your medical conditions including if you:

- have or have had symptoms of acute pancreatitis, stones in your gallbladder, or a history of alcoholism.
- have or have had liver or kidney problems.
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take a TZD (thiazolidinediones).
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant, or plan to become pregnant. It is not known if SOLIQUA 100/33 will harm your unborn baby. Tell your healthcare provider if you are pregnant or plan to become pregnant while using SOLIQUA 100/33.
- are breastfeeding or plan to breastfeed. It is not known if SOLIQUA 100/33 passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you use SOLIQUA 100/33.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SOLIQUA 100/33 may affect the way some medicines work and some medicines may affect the way SOLIQUA 100/33 works.

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Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use SOLIQUA 100/33?

- Read all the detailed **Instructions for Use** that come with SOLIQUA 100/33 for instructions on using the

SOLIQUA 100/33 pen and injecting SOLIQUA 100/33.

- Use SOLIQUA 100/33 exactly as your healthcare provider tells you to.
- Do not change your dose unless your healthcare provider has told you to change your dose.
- Your healthcare provider should teach you how to inject SOLIQUA 100/33 before you use it for the first time. If you have questions or do not understand the instructions, talk to your healthcare provider.
- Take SOLIQUA 100/33 only 1 time each day within 1 hour before the first meal of the day.
- If you miss a dose of SOLIQUA 100/33, take your next scheduled dose at your regular time. **Do not** take an extra dose or increase your dose to make up for the missed dose.
- Check the label on the SOLIQUA 100/33 pen each time you give your injection to make sure you are using the correct medicine.
- **Do not take more than 60 units of SOLIQUA 100/33 each day.** SOLIQUA 100/33 contains two medicines: insulin glargine and lixisenatide. If you take too much SOLIQUA 100/33, it can cause severe nausea and vomiting. Do not take SOLIQUA 100/33 with other GLP-1 receptor agonists. If you take too much SOLIQUA 100/33, call your healthcare provider or go to the nearest hospital emergency room right away.
- Only use SOLIQUA 100/33 that is clear, colorless to almost colorless. If you see small particles, return it to your pharmacy for a replacement.
- 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).
- Inject your dose of SOLIQUA 100/33 under the skin (subcutaneously) of your abdomen, thigh or upper arm. Do not use SOLIQUA 100/33 in an insulin pump or inject SOLIQUA 100/33 into your vein (intravenously) or muscle (intramuscularly).
- **Do not** mix SOLIQUA 100/33 in any other type of insulin or liquid medicine prior to injection.
- **Do not** remove SOLIQUA 100/33 from the throw away (disposable) prefilled pen with a syringe.
- **Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.**
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

Your dose of SOLIQUA 100/33 may need to change because of a change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of SOLIQUA 100/33?

SOLIQUA 100/33 may cause serious side effects including:

- **See "What is the most important information I should know about SOLIQUA 100/33?"**
- **Severe allergic reactions.** Severe allergic reactions can happen with SOLIQUA 100/33. Stop taking SOLIQUA 100/33 and get medical help right away if you have any symptoms of a severe allergic reaction. See **"Who should not use SOLIQUA 100/33?"**
- **Low blood sugar (hypoglycemia). Your risk for getting low blood sugar is higher if you take another medicine that can cause low blood sugar.** Signs and symptoms of low blood sugar include:
  - headache
  - dizziness
  - drowsiness
  - confusion
  - weakness
  - irritability
  - hunger
  - sweating
  - fast heartbeat
  - feeling jittery

Talk with your healthcare provider about how to treat low blood sugar.

- **Kidney problems (kidney failure)**. In people who have kidney problems, the occurrence of diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called TZDs with SOLIQUA 100/33 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with SOLIQUA 100/33. Your healthcare provider should monitor you closely while you are taking TZDs with SOLIQUA 100/33. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, swelling of your ankles or feet, sudden weight gain.
  Treatment with TZDs and SOLIQUA 100/33 may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

The most common side effects of SOLIQUA 100/33 may include:

- low blood sugar (hypoglycemia)
- allergic reactions

- nausea
- headache
- stuffy or runny nose and sore throat
- diarrhea
- upper respiratory tract infection

Nausea and diarrhea usually happen more often when you start using **SOLIQUA 100/33**.

These are not all the possible side effects of SOLIQUA 100/33. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SOLIQUA 100/33?

- Store your new, unused SOLIQUA 100/33 SoloStar® pen in the refrigerator at 36°F to 46°F (2°C to 8°C). Protect the pen from light.
- After first use, store your SOLIQUA 100/33 pen at room temperature no higher than 86°F (30°C).
- Do not freeze SOLIQUA 100/33 pens and do not use SOLIQUA 100/33 if it has been frozen.
- Replace the pen cap after each use to protect from light.
- After first use, use the SOLIQUA 100/33 pen for up to 14 days. Throw away the used SOLIQUA 100/33 pen after 14 days, even if there is some medicine left in the pen.
- Do not use SOLIQUA 100/33 past the expiration date printed on the label of the carton and pen.
- Do not store the SOLIQUA 100/33 pen with the needle attached. If the needle is left on, this might lead to contamination and cause air bubbles which might affect your dose of medicine.
- See the **Instructions for Use** about the right way to throw away the SOLIQUA 100/33 pen.
- **Keep your SOLIQUA 100/33 pen, pen needles, and all medicines out of the reach of children.**

General information about the safe and effective use of SOLIQUA 100/33.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** use SOLIQUA 100/33 for a condition for which it was not prescribed. Do not give SOLIQUA 100/33 to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about SOLIQUA 100/33 that is written for health professionals.

What are the ingredients in SOLIQUA 100/33?

Active ingredients: insulin glargine and lixisenatide

Inactive ingredients: 3 mg of methionine, 2.7 mg of metacresol, 20 mg of glycerol, 30 mcg of zinc, hydrochloric acid, sodium hydroxide and water for injection.

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For more information, go to www.soliqua100-33.com or call sanofi-aventis 1-800-633-1610.
This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: November 2016