avoid fluid depletion. SOLIQUA 100/33 is not recommended in patients with end-stage renal disease *[see Use in Specific Populations (8.6)]*.

5.8 Immunogenicity

Patients may develop antibodies to insulin and lixisenatide, components of SOLIQUA 100/33, following treatment. A pooled analysis of studies of lixisenatide-treated patients showed that 70% were antibody positive at Week 24. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection-site reactions occurred in antibody positive patients *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.

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.

5.9 Hypokalemia

All insulin-containing products, including SOLIQUA 100/33, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.10 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin-containing products, including SOLIQUA 100/33. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin-containing products, including SOLIQUA 100/33, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.11 Macrovascular Outcomes

There have been no clinical studies establishing macrovascular risk reduction with SOLIQUA 100/33.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Anaphylaxis and Serious Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.6)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.7)]*
- Hypokalemia *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The safety of SOLIQUA 100/33 (n=834, with a mean treatment duration of 203 days) has been evaluated in two clinical studies (30 weeks duration) in type 2 diabetes patients. The studies, Study A and B *[see Clinical Studies (14)]*, had the following characteristics: mean age was approximately 59 years; approximately 50% were male, 90% were Caucasian, 6% were Black or African American, and 18% were Hispanic. The mean duration of diabetes was 10.3 years, mean HbA1c at screening for Study A was 8.2 and Study B was 8.5. The mean BMI at baseline was 32 kg/m^2. Baseline eGFR was ≥60 mL/min in 87.2% of the pooled study population and mean baseline eGFR was 83.0 mL/min/1.73 m^2.

Table 3: Adverse Reactions Occurring in ≥5% of SOLIQUA 100/33–Treated Patients with Type 2 Diabetes Mellitus from Two Pooled Clinical Trials

	SOLIQUA 100/33, % (n=834)
Nausea	10.0
Nasopharyngitis	7.0
Diarrhea	7.0
Upper respiratory tract infection	5.5
Headache	5.4

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, and insulin-containing products including SOLIQUA 100/33 *[see Warnings and Precautions (5.6)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for SOLIQUA 100/33 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the SOLIQUA 100/33 program, severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 70 mg/dL (see Table 4).

No clinically important differences in risk of severe hypoglycemia between SOLIQUA 100/33 and comparators were observed in clinical trials.

Table 4: Hypoglycemic Episodes in SOLIQUA-Treated Patients with T2DM

	SOLIQUA 100/33 Study A N=469	**SOLIQUA 100/33 Study B N=365**
Severe symptomatic hypoglycemia* (%)	0	1.1
Hypoglycemia (self-monitored plasma glucose <54 mg/dL) (%)	8.1	17.8

* Defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions are the most commonly observed adverse reaction in patients using lixisenatide. Gastrointestinal adverse reactions occur more frequently at the beginning of SOLIQUA 100/33 therapy. Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension, and decreased appetite have been reported in patients treated with SOLIQUA 100/33.

In Study A, vomiting was 6.4% in the lixisenatide-treated patients versus 3.2% in the SOLIQUA 100/33–treated patients and 1.5% in the insulin glargine–treated patients; nausea was 24% in the lixisenatide-treated patients versus 9.6% in the SOLIQUA 100/33–treated patients, and 3.6% in the insulin glargine–treated patients.

Lipodystrophy

Administration of insulin subcutaneously, including SOLIQUA 100/33, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients *[see Dosage and Administration (2.5)]*.

Anaphylaxis and Hypersensitivity

Lixisenatide

In the lixisenatide development program anaphylaxis cases were adjudicated. Anaphylaxis was defined as a skin or mucosal lesion of acute onset associated with at least 1 other organ system involvement. Symptoms such as hypotension, laryngeal edema or severe bronchospasm could be present but were not required for the case definition. More cases adjudicated as meeting the definition for anaphylaxis occurred in lixisenatide-treated patients (incidence rate of 0.2% or 16 cases per 10,000 patient years) than placebo-treated patient (incidence rate of 0.1% or 7 cases per 10,000 patient years).

Allergic reactions (such as anaphylactic reaction, angioedema, and urticaria) adjudicated as possibly related to the study medication were observed more frequently in lixisenatide-treated patients (0.4%) than placebo-treated patients (0.2%) *[see Warnings and Precautions (5.1)]*.

Insulin glargine

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including SOLIQUA 100/33, and may be life threatening.

Injection-Site Reactions

As with any insulin or GLP-1 receptor agonist–containing product, patients taking SOLIQUA 100/33 may experience injection-site reactions, including injection-site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection-site mass. In the clinical program the proportion of injection-site reactions occurring in patients treated with SOLIQUA 100/33 was 1.7%.

Insulin Initiation and Intensification of Glucose Control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Some patients taking insulin glargine, a component of SOLIQUA 100/33 have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Weight Gain

Weight gain can occur with insulin-containing products, including SOLIQUA 100/33, and has been attributed to the anabolic effects of insulin.

6.2 Immunogenicity

SOLIQUA 100/33

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLIQUA 100/33 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

After 30 weeks of treatment with SOLIQUA 100/33 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%.

Lixisenatide

In the pool of 9 placebo-controlled studies, 70% of patients exposed to lixisenatide tested positive for anti-lixisenatide antibodies during the trials. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection-site reactions occurred in antibody positive patients *[see Warnings and Precautions (5.8)]*.

Anti-lixisenatide antibody characterization studies have demonstrated the potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon, but their incidence has not been fully determined and the clinical significance of these antibodies is not currently known.

No information regarding the presence of neutralizing antibodies is currently available.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

7 DRUG INTERACTIONS

7.1 Medications that Can Affect Glucose Metabolism

A number of medications affect glucose metabolism and may require dose adjustment of SOLIQUA 100/33 and particularly close monitoring.

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

7.2 Effects of Delayed Gastric Emptying on Oral Medications

Lixisenatide-containing products, including SOLIQUA 100/33, delay gastric emptying which may reduce the rate of absorption of orally administered medications. Use caution when coadministering oral medications that have a narrow therapeutic ratio or that require careful clinical monitoring. These medications should be adequately monitored when concomitantly administered with lixisenatide. 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.

- Antibiotics, acetaminophen, or other medications that are particularly dependent on threshold concentrations for efficacy or for which a delay in effect is undesirable should be administered at least 1 hour before SOLIQUA 100/33 injection *[see Clinical Pharmacology (12.3)]*.
- Oral contraceptives should be taken at least 1 hour before SOLIQUA 100/33 administration or 11 hours after *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide, a component of SOLIQUA 100/33, during pregnancy. SOLIQUA 100/33 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The limited available data with SOLIQUA 100/33 and lixisenatide in pregnant women is not sufficient to inform a drug-associated risk of major birth defects and miscarriage. Published studies with insulin glargine use during pregnancy have not reported a clear association with insulin glargine and major birth defect or miscarriage risk *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure and skeletal defects at systemic exposures that decreased maternal food intake and weight gain during gestation, and that are 1-time and 6-times higher than the 20 mcg/day highest clinical dose, respectively, based on plasma AUC *[see Data]*.

The estimated background risk of major birth defects is 6%-10% in women with pregestational diabetes with a HbA1c >7 and has been reported to be as high as 20%-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human data

Insulin glargine

Published data do not report a clear association with insulin glargine and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin glargine is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including small sample size and some lacking comparator groups.

Animal data

Animal reproduction studies were not conducted with the combined products in SOLIQUA 100/33. The following data are based on studies conducted with the individual components of SOLIQUA 100/33.

Lixisenatide

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg during organogenesis (gestation day 6 to 17), fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥2.5 mcg/kg/dose, resulting in systemic exposure that is 1-time the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of 0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg during organogenesis (gestation day 6 to 18), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at ≥5 mcg/kg/day or systemic exposures that are 6-times the 20 mcg/day highest clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of ≤0.3%. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 0.15, 1.0, and 2.5 mcg/kg administered during organogenesis, resulting in systemic exposures up to 9-times the clinical exposure at 20 mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, and motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at 400 mcg/kg/day, which is approximately 200-times the 20 mcg/day clinical dose based on mcg/m^2.

Insulin glargine

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 2-times the recommended human subcutaneous high dose of 60 units/day (0.0364 mg/kg/day), based on mg/m^2. In rabbits, doses up to 0.072 mg/kg/day, which is approximately 1-times the maximum recommended human subcutaneous dose of 60 units/day (0.0364 mg/kg/day), based on mg/m^2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lixisenatide and insulin glargine in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. Lixisenatide is present in rat milk *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOLIQUA 100/33 and any potential adverse effects on the breastfed child from SOLIQUA 100/33 or from the underlying maternal condition.

Data

Lixisenatide

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.01%) levels of unchanged lixisenatide peptide in the gastric contents of weaning offspring.

8.4 Pediatric Use

Safety and effectiveness of SOLIQUA 100/33 have not been established in pediatric patients below 18 years of age.

8.5 Geriatric Use

Of the total number of subjects (n=834) in controlled clinical studies of patients with type 2 diabetes, who were treated with SOLIQUA 100/33, 25.2% (n=210) were ≥65 years of age and 4% (n=33) were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.

Nevertheless, caution should be exercised when SOLIQUA 100/33 is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

8.6 Renal Impairment

Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with renal impairment *[see Warnings and Precautions (5.7)]*.

Insulin Glargine

Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure.

Lixisenatide

In patients with mild and moderate renal impairment no dose adjustment is required but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because of higher incidences of hypoglycemia, nausea and vomiting that were observed in these patients. Increased gastrointestinal adverse reactions may lead to dehydration and acute renal failure and worsening of chronic failure in these patients.

Clinical experience in patients with severe renal impairment is limited as there were only 5 patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) exposed to lixisenatide in all controlled studies. Lixisenatide exposure was higher in these patients *[see Clinical Pharmacology (12.3)]*. Patients with severe renal impairment exposed to lixisenatide should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes in renal function.

There is no therapeutic experience in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use SOLIQUA 100/33 in this population.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of SOLIQUA 100/33 has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.

8.8 Patients with Gastroparesis

Lixisenatide, one of the components of SOLIQUA 100/33, slows gastric emptying. Patients with preexisting gastroparesis were excluded from clinical trials of SOLIQUA 100/33. SOLIQUA 100/33 is not recommended in patients with severe gastroparesis.

10 OVERDOSAGE

Insulin Glargine

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.6, 5.9)]*. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

Lixisenatide

During clinical studies, doses up to 30 mcg of lixisenatide twice daily (3 times the daily recommended dose) were administered to type 2 diabetic patients in a 13-week study. An increased incidence of gastrointestinal disorders was observed.

In case of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and the SOLIQUA 100/33 dose should be reduced to the prescribed dose.

11 DESCRIPTION

SOLIQUA 100/33 (insulin glargine and lixisenatide injection), for subcutaneous use, is a combination of a long-acting basal insulin analog, insulin glargine, and a GLP-1 receptor agonist, lixisenatide.

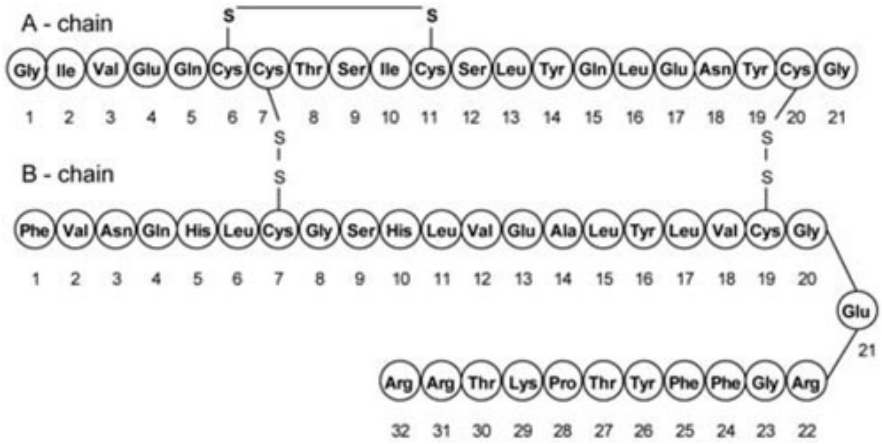
Each SOLIQUA 100/33 prefilled single-patient-use disposable pen contains 300 units of insulin glargine and 100 mcg of lixisenatide in 3 mL of a clear, colorless to almost colorless, sterile, and aqueous solution. Each mL of solution contains 100 units insulin glargine and 33 mcg lixisenatide.

SOLIQUA 100/33 contains the following inactive ingredients (per mL): 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.

Insulin Glargine

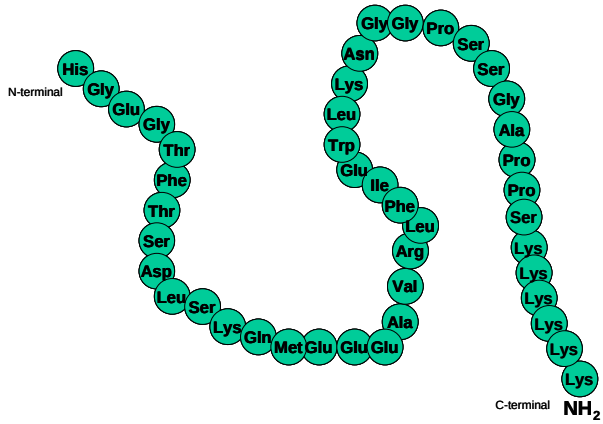
Insulin glargine is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin

glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added at the C-terminus of the B-chain. Insulin glargine has low aqueous solubility at neutral pH. At pH 4 insulin glargine is completely soluble. Chemically, insulin glargine is 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063. Insulin glargine has the following structural formula:



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

Table 5: Results at 30 Weeks – Add-On to Metformin Clinical Study

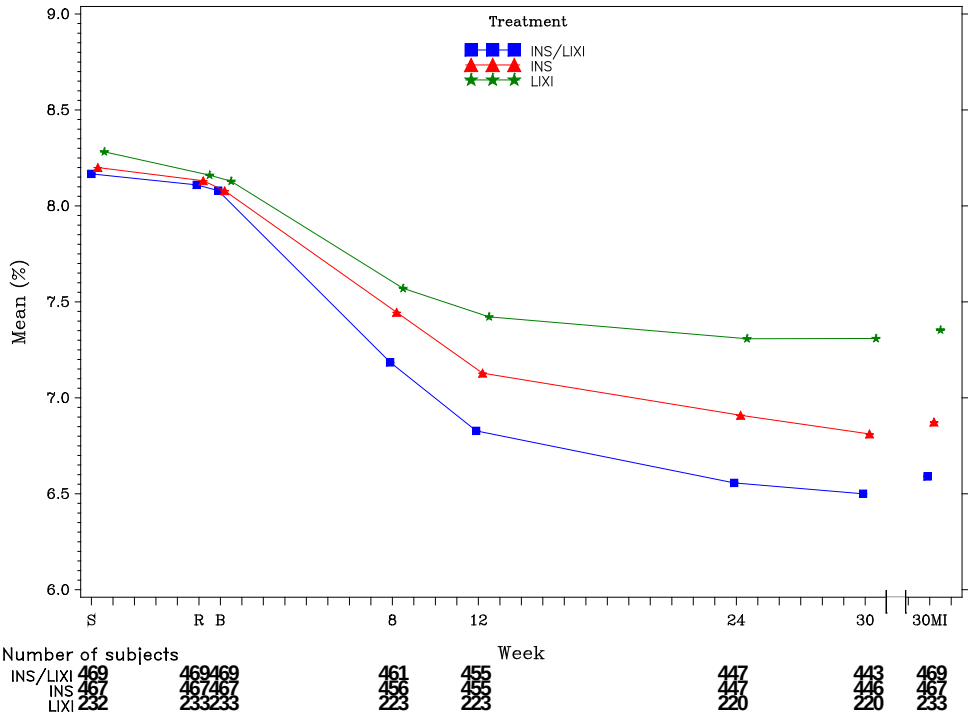
	SOLIQUA 100/33	Insulin Glargine 100 units/mL	Lixisenatide
Number of subjects (randomized and treated)	469	467	233
HbA1c (%)			
Baseline (mean; post run-in phase)	8.1	8.1	8.1
End of study (mean)	6.5	6.8	7.3
LS change from baseline (mean)*	-1.6	-1.3	-0.9
LS mean difference vs insulin glargine [95% confidence interval] (p-value)	-0.3 [-0.4, -0.2]† (<0.0001)		–
LS mean difference vs lixisenatide [95% confidence interval] (p-value)	–	–	-0.7 [-0.8, -0.6]‡ (<0.0001)
Number of Patients (%) reaching HbA1c <7% at week 30	345 (74%)	277 (59%)	76 (33%)
Fasting plasma glucose (mg/dL)			
Baseline (mean)	177.9	175.7	175.8
End of study (mean)	113.9	117.6	149.0
LS change from baseline (mean)	-59.1	-55.8	-27.2

* Estimated using an ANCOVA with treatment, randomization strata, and country as fixed factors and baseline HbA1c as covariate. Twenty-six (5.5%) patients in the SOLIQUA 100/33 arm and 21 (4.5%) patients in the insulin glargine 100 units/mL arm, and 13 (5.6%) patients in the lixisenatide arm had missing HbA1c measurement at Week 30. Missing measurements were imputed using multiple imputations with respect to the baseline value of the subject.

† 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 were 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 at week 30 was 39.8 units (for SOLIQUA 100/33: 39.8 units insulin glargine/13.1 mcg lixisenatide) and 40.5 units in the insulin glargine–treated patients. 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.

‡ Lixisenatide was given at the maintenance dose of 20 mcg.

Figure 1: Mean HbA1c (%) Over Time – Randomized and Treated Population



S = Screening (Week 6), R = Run-in (Week 1), B = Baseline, MI = Multiple imputation.
INS/LIXI = fixed ratio combination, INS = Insulin Glargine, LIXI = Lixisenatide
Note: The plot included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue medication.
30MI: Missing HbA1c values at Week 30 in each group were imputed using their baseline HbA1c values plus an error. The error is normally distributed with mean zero and a standard deviation set equal to the estimated pooled standard deviation.

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

A total of 736 patients with type 2 diabetes participated in a randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study (Study B: NCT02058160) 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 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% 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 m^2 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 6 for the other endpoints in the study.

Table 6: 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. Twenty (5.5%) patients in the SOLIQUA 100/33 arm and 10 (2.7%) patients in the insulin glargine 100 units/mL arm had missing HbA1c measurement at Week 30. Missing measurements were imputed using multiple imputations with respect 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 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 single-patient-use 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

Dispense in the original sealed carton with the enclosed Instructions for Use.

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 77°F (25°C). Replace the pen cap after each use to protect from light.

Discard pen 28 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 *[see Warnings and Precautions (5.3)]*.

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 *[see Warnings and Precautions (5.6)]*. 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 insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.4)]*.

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 *[see Warnings and Precautions (5.5)]*.

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)]*.

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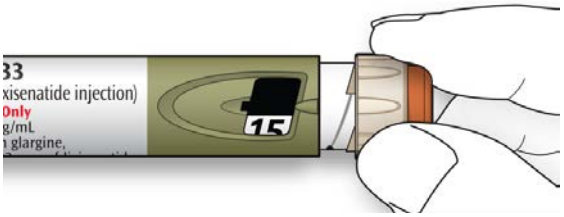
- **Do not** select a dose or press the injection button without a needle attached. This may damage your pen.
- **Only use this pen to inject your daily dose from 15 to 60 units. Do not change your dose unless your healthcare provider has told you to change your dose.**
- **Do not** use this pen if you 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.

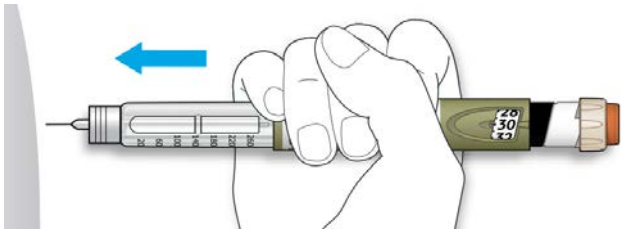
Step 5: Inject your dose

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."

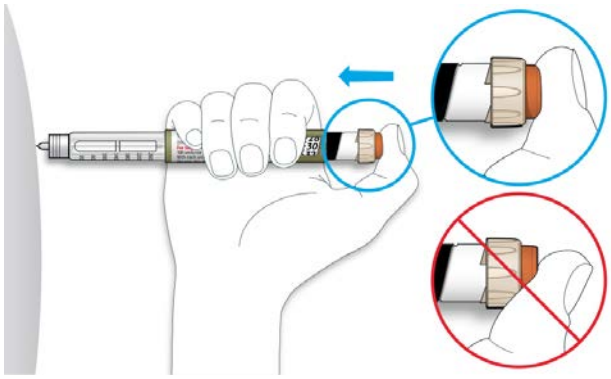
5B Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



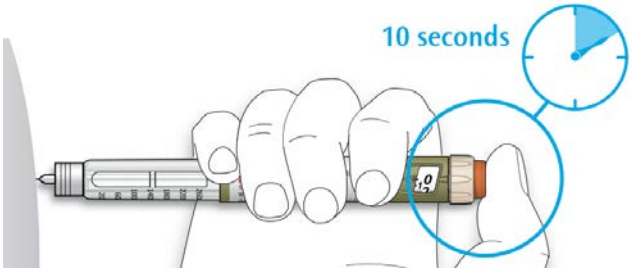
5C Place your thumb on the injection button. Then press all the way in and hold.

- **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:

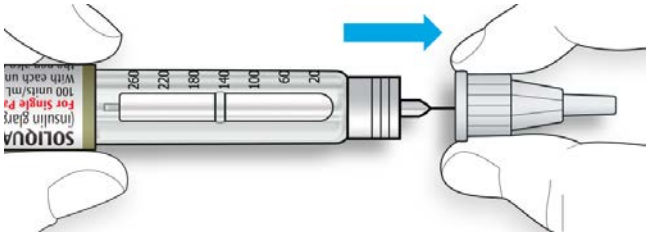
- Change the needle (**see Step 6** to remove the needle **and Step 2** to attach a new needle) then do a safety test (**see Step 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove medicine from your pen.

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.

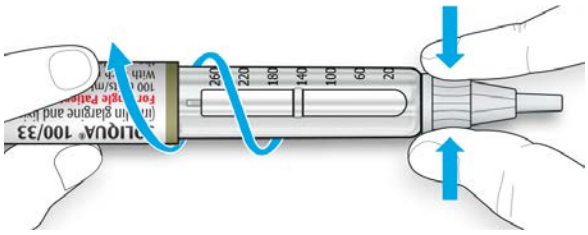
6A **Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back. Then push firmly on.**

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

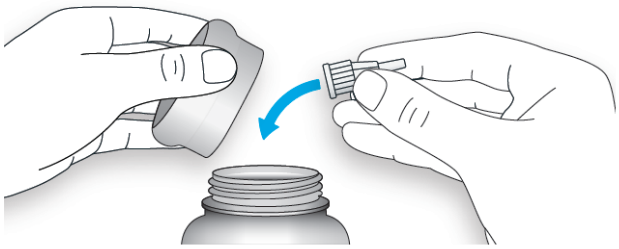


6B **Grip and squeeze the widest part of the outer needle cap.** Turn your pen several times with your other hand to remove the needle.

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

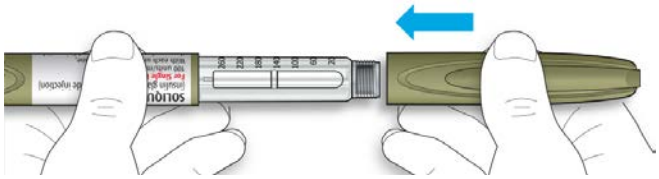


6C **Throw away the used needle in a puncture-resistant container** (see "**Throwing your pen away**" at the end of this Instructions for Use).



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 **28 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 77°F (25°C).**
- **Do not** put your pen back in the refrigerator.
- **Do not** store your pen with the needle attached.
- Store the pen with your pen cap on.

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

How to care for your pen

Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- If you think that your pen may be damaged, **do not** try to fix it. Use a new one.

Protect your pen from dust and dirt

- You can clean the outside of your pen by wiping it with a damp cloth (water only). **Do not** soak, wash or lubricate the pen. This may damage it.

Throwing your pen away

- 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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