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

1 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.

2 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)

3 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)

4 CONTRAINDICATIONS

• Discontinue SOLIQUA 100/33 in patients with severe hypersensitivity (anaphylaxis) reactions 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)
• Immune monitoring: 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)

5 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.

6 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)

7 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 Medication Guide

Revised: 10/2017
**FULL PRESCRIBING INFORMATION**

1 INDICATIONS AND USAGE

SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

Limitations of Use:
- SOLIQUA 100/33 has not been studied in patients with a history of pancreatitis [see Warnings and Precautions (5.2)]. Consider other anti-diabetic therapies in patients with a history of pancreatitis.
- SOLIQUA 100/33 is not recommended for use in combination with any other product containing lixisenatide or another GLP-1 receptor agonist [see Warnings and Precautions (5.5)].
- SOLIQUA 100/33 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- SOLIQUA 100/33 has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.
- SOLIQUA 100/33 has not been studied in combination with prandial insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

The following are important dosing information for SOLIQUA 100/33, a combination of insulin glargine and lixisenatide:

- Discontinue therapy with lixisenatide or basal insulin prior to initiation of SOLIQUA 100/33.
- In patients inadequately controlled on 30 to 60 units of basal insulin, the recommended starting dosage of SOLIQUA 100/33 is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
- In patients inadequately controlled on 30 to 60 units of basal insulin, the recommended starting dosage of SOLIQUA 100/33 is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily.
- Administer SOLIQUA 100/33 subcutaneously once a day within the hour prior to the first meal of the day.
- The maximum dosage of SOLIQUA 100/33 is 60 units (60 units insulin glargine/20 mcg lixisenatide) [see Warnings and Precautions (5.5)].
- The SOLIQUA 100/33 pen delivers doses from 15 to 60 units in a single injection [see Table 1] [see Dosage and Administration (2.2)].
- Use alternative antidiabetic products if patients require a SOLIQUA 100/33 daily dosage:
  - below 15 units, or
  - over 60 units

Table 1 presents the units insulin glargine and the micrograms of lixisenatide in each dosage of SOLIQUA 100/33.

Table 1: Units of Insulin Glargine and Micrograms of Lixisenatide in Each Dosage of SOLIQUA 100/33

<table>
<thead>
<tr>
<th>SOLIQUA 100/33 (dose window display)</th>
<th>Insulin glargine component dose</th>
<th>Lixisenatide component dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>---</td>
<td>---</td>
<td>Safety test dose – not for injection</td>
</tr>
<tr>
<td>15</td>
<td>15 units</td>
<td>5 mcg</td>
<td>Recommended starting dosage for patients previously treated with lixisenatide or less than 30 units of basal insulin</td>
</tr>
<tr>
<td>16</td>
<td>16 units</td>
<td>5.3 mcg</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>17 units</td>
<td>5.7 mcg</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18 units</td>
<td>6 mcg</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19 units</td>
<td>6.3 mcg</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20 units</td>
<td>6.7 mcg</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>21 units</td>
<td>7 mcg</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>22 units</td>
<td>7.3 mcg</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>23 units</td>
<td>7.7 mcg</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>24 units</td>
<td>8 mcg</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>25 units</td>
<td>8.3 mcg</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>26 units</td>
<td>8.7 mcg</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>27 units</td>
<td>9 mcg</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>28 units</td>
<td>9.3 mcg</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>29 units</td>
<td>9.7 mcg</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>30 units</td>
<td>10 mcg</td>
<td>Recommended starting dosage for patients previously treated with 30 to 60 units of basal insulin</td>
</tr>
<tr>
<td>31</td>
<td>31 units</td>
<td>10.3 mcg</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>32 units</td>
<td>10.7 mcg</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>33 units</td>
<td>11 mcg</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>34 units</td>
<td>11.3 mcg</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>35 units</td>
<td>11.7 mcg</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>36 units</td>
<td>12 mcg</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>37 units</td>
<td>12.3 mcg</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>38 units</td>
<td>12.7 mcg</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>39 units</td>
<td>13 mcg</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>40 units</td>
<td>13.3 mcg</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>41 units</td>
<td>13.7 mcg</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>42 units</td>
<td>14 mcg</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>43 units</td>
<td>14.3 mcg</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>44 units</td>
<td>14.7 mcg</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>45 units</td>
<td>15 mcg</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>46 units</td>
<td>15.3 mcg</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>47 units</td>
<td>15.7 mcg</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>48 units</td>
<td>16 mcg</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>49 units</td>
<td>16.3 mcg</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>50 units</td>
<td>16.7 mcg</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>51 units</td>
<td>17 mcg</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>52 units</td>
<td>17.3 mcg</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>53 units</td>
<td>17.7 mcg</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>54 units</td>
<td>18 mcg</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>55 units</td>
<td>18.3 mcg</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>56 units</td>
<td>18.7 mcg</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>57 units</td>
<td>19 mcg</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>58 units</td>
<td>19.3 mcg</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>59 units</td>
<td>19.7 mcg</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>60 units</td>
<td>20 mcg</td>
<td>Maximum daily dosage [see Warnings and Precautions (5.5)]</td>
</tr>
</tbody>
</table>

*The dose window on the SOLIQUA 100/33 pen displays numbers for the even units and displays lines for the odd units.

2.2 Titration of SOLIQUA 100/33

After starting with the recommended dosage of SOLIQUA 100/33, based upon prior insulin dose or lixisenatide use [see Dosage and Administration (2.1)], titrate the dosage upwards or downwards by two to four units (see Table 2) every week based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved. The dosage of SOLIQUA 100/33 is between 15 to 60 units (see Table 1).

- To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications [see Warnings and Precautions (5.4) and Drug Interactions (7)].

Table 2: Recommended Titration of SOLIQUA 100/33 (Every Week)*

<table>
<thead>
<tr>
<th>Self-Monitored Fasting Plasma Glucose</th>
<th>SOLIQUA 100/33 Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above target range</td>
<td>+2 units (2 units of insulin glargine and 0.66 mcg of lixisenatide) to +4 units (4 units insulin glargine and 1.32 mcg lixisenatide)</td>
</tr>
<tr>
<td>Within target range</td>
<td>0 units</td>
</tr>
<tr>
<td>Below target range</td>
<td>-2 units (2 units of insulin glargine and 0.66 mcg of lixisenatide) to -4 units (4 units insulin glargine and 1.32 mcg lixisenatide)</td>
</tr>
</tbody>
</table>

*The recommended SOLIQUA 100/33 dosage is between 15 to 60 units (see Table 1)

2.3 Missed Doses

Instruct patients who miss a dose of SOLIQUA 100/33 to resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.
5.4 Hypo-/Hyperglycemia

SOLIQUA 100/33 contains two drugs: insulin glargine and lixisenatide. Administration of more than 60 units of SOLIQUA 100/33 daily can result in overdose of the lixisenatide component. Do not exceed the maximum recommended dose of SOLIQUA 100/33.

5.5 Overdose Due to Medication Errors

Anaphylaxis and Serious Hypersensitivity Reactions

In clinical trials of lixisenatide, a component of SOLIQUA 100/33, there have been cases of anaphylaxis (frequency of 0.1% or 10 cases per 10,000 patient-years) and other serious hypersensitivity reactions including angioedema. Severe, life-threatening, generalized allergic reactions, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock can occur with insulins, including insulin glargine, a component of SOLIQUA 100/33 (see Adverse Reactions (6.1)). Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with lixisenatide. SOLIQUA 100/33 is contraindicated in patients with known hyper-sensitivity to lixisenatide or insulin glargine (see Contraindications (4) and Adverse Reactions (6.1)).

5.6 Hypokalemia

Hypokalemia occurs in 5.6% of patients treated with GLP-1 receptor agonists, such as lixisenatide, and may be 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 may be considered.

5.11 Macrovascular Outcomes

There have been no clinical studies establishing macrovascular risk reduction with SOLIQUA 100/33 or any other antidiabetic drug.

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 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 8.5. The mean BMI at baseline was 32 kg/m². Baseline eGFR was 60 mL/min in 87.2% of the pooled study population and mean baseline eGFR was 85.0 mL/min/1.73 m².

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

<table>
<thead>
<tr>
<th>SOLIQUA 100/33, % (n=834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea 10.0</td>
</tr>
<tr>
<td>Nasopharyngitis 7.0</td>
</tr>
<tr>
<td>Diarrhea 7.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection 5.5</td>
</tr>
<tr>
<td>Headache 5.4</td>
</tr>
</tbody>
</table>

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 (6.5)). 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 this reason, comparing rates of hypoglycemia in clinical trials for SOLIQUA 100/33 with the incidence of hypoglycemia from other studies 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: Severe or Documented Symptomatic Hypoglycemic Episodes in SOLIQUA-Treated Patients with T2DM

<table>
<thead>
<tr>
<th>SOLIQUA 100/33</th>
<th>SOLIQUA 100/33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A N=469</td>
<td>Study B N=365</td>
</tr>
<tr>
<td>Severe symptomatic hypoglycemia (%)</td>
<td>0</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycemia (%)</td>
<td>25.6</td>
</tr>
</tbody>
</table>

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

Gastrointestinal Adverse Reactions

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.

Lipodystrophy

Administration of insulin subcutaneously, including SOLIQUA 100/33, has resulted in lipodystrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients (see Dosage and Administration (2.4)).

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 gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension and decreased appetite have been reported in patients treated with SOLIQUA 100/33.

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.

### 6.5 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 mIU/mL), 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)).

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.

### 7.0 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.

<table>
<thead>
<tr>
<th>Drugs That May Increase the Risk of Hypoglycemia</th>
<th>Drugs</th>
<th>Intervention</th>
<th>Detected Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, diacylglycerol, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonylurea antibiotics.</td>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, diacylglycerol, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonylurea antibiotics.</td>
<td>Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.</td>
<td>Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs That May Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33</th>
<th>Drugs</th>
<th>Intervention</th>
<th>Detected Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 adrenergic blockers, beta-blockers, calcium channel blockers, clonidine, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
<td>Alpha-1 adrenergic blockers, beta-blockers, calcium channel blockers, clonidine, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
<td>Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.</td>
<td>Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.</td>
</tr>
</tbody>
</table>

#### 7.2 Effects of Delayed Gastric Emptying on Oral Medications

Lixisenatide delays 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)).

### 8.0 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 are 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 mg/daily clinical dose, respectively, based on plasma AUC (see Data).

The estimated background risk of major birth defects is 6%-10% in women with pre-gestational diabetes with an 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 embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortion, preterm delivery, still birth 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 a 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, twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg during organogenesis (gestation days 6 to 18) were present with multiple visceral and skeletal malformations, including closure defects, at ≥25 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 rat fetuses is low with a concentration ratio of 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 ≥25 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 of 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 2.0, 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 mg/m².

Insulin Glargine

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Japanese monkeys. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mcg/m²/hour, which is approximately 2.5 times the recommended human subcutaneous high dose of 0.0364 mg/kg/day, based on mg/m².

In rabbits, doses up to 0.072 mcg/kg/day, which is approximately 1.5 times the maximum recommended human subcutaneous dose of 60 units/day (0.0054 mcg/kg/day), based on mg/m², 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 dilatation 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 (0.4%) 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 ≥75 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 the potential for accumulation of hypoglycemia, nausea, and vomiting that was 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 m²) 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 m²), 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 (5.8, 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 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 aspartagine 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, but is highly soluble at pH 4. Human insulin glargine is completely soluble. Chemically, insulin glargine is 21-Gly30-Lys30-Arg30-bL-Arg-human insulin and has the empirical formula C₂₃H₂₄N₆O₆S₂ with a molecular weight of 6063. Insulin glargine has the following structural formula:

[Image of 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 C₂₃H₂₄N₆O₆S with the following chemical structure:

[Image of chemical structure]
Lixisenatide

In a clinical pharmacology study in adults with type 2 diabetes mellitus, lixisenatide reduced fasting plasma glucose and postprandial blood glucose AUC(0–300min) 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 among once daily reduced postprandial glucagon levels (AUC(0–60min) 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 21% while the C_{min} was decreased by 63%. The AUC and C_{max} of the active metabolite (rapamill) were not affected. The t_{max} of rapamill and rapamill 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

Lixisenatide was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells ( Ames- and HSGPT-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, which was approximately 2-times the recommended human subcutaneous maximum dose of 60 units/day (0.0364 mg/kg/day), based on mg/kg, 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.

Rapamill

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 mg/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 mg/day based on plasma AUC. A numerical increase in thyroid C-cell carcinomas was observed in rats at ≥600 mcg/kg/day, resulting in systemic exposures that are ≥56-times the human exposure achieved at 20 mg/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 microcytosis).

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 mg/day based on mg/kg.

14 CLINICAL STUDIES

A total of 736 patients with type 2 diabetes participated in a randomized, 30-week, active-controlled, 1:1, 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 an A1C of 0.4% or less. The mean exposure was approximately 2-times and for the mouse approximately 2-times the human exposure achieved at 20 mg/day based on plasma AUC. The mean exposure was approximately 2-times and for the mouse approximately 2-times the human exposure achieved at 20 mg/day based on plasma AUC.

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 dose of insulin glargine at baseline was 35 units. The maximum dose of insulin glargine daily dose of 20 to 50 units (mean of 35 units), were randomized to either SOLIQUA or insulin glargine 100 units/mL. 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 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 was decreased during run-in period from 8.5% to 8.1%. Any other OADs were discontinued.

The mean eGFR ≥60 mL/min. After screening, eligible patients (n=1018) entered a 6-week run-in phase where patients remained on or 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 was decreased during run-in period from 8.5% to 8.1%. Any other OADs were discontinued.

At baseline, patients with an HbA1c between 7% and 10% and an A1C of 0.4% or less. The mean exposure was approximately 2-times and for the mouse approximately 2-times the human exposure achieved at 20 mg/day based on plasma AUC. The mean exposure was approximately 2-times and for the mouse approximately 2-times the human exposure achieved at 20 mg/day based on plasma AUC. The mean exposure was approximately 2-times and for the mouse approximately 2-times the human exposure achieved at 20 mg/day based on plasma AUC.
Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) before each injection. This prevents contamination and/or infection, or leakage of the SOLIQUA 100/33 pen, and ensures accurate dosing. Always use a new needle for each injection to prevent contamination. 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 ensures accurate dosing. Always use a new needle for each injection to prevent contamination.

**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:

<table>
<thead>
<tr>
<th>Dosage Unit/Strength</th>
<th>Package size</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mL SOLIQUA 100/33 disposable prefilled pen 100 units/mL insulin glargine and 33 mcg/mL lixisenatide</td>
<td>Package of 5</td>
<td>0024-5671-05</td>
</tr>
</tbody>
</table>

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 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 ensures accurate dosing. Always use a new needle for each injection to prevent contamination.

**17 PATIENT COUNSELING INFORMATION**

Advising patients 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 (5.5)]. 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 (5.6)]. 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. Hypoglycemia or Hyperglycemia: 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.

Advising patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advising 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.

Management of Hypoglycemia and Handling of Special Situations: Instruct patients on self-management procedures including glucose monitoring and management of hypoglycemia and hyperglycemia. Inform 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)].

SOLIQUA and SoloStar are registered trademarks of sanofi-aventis U.S. LLC.

Approved: October 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.

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)
- nausea
- headache
- stuffy or runny nose and sore throat
- allergic reactions
- 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 77°F (25°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 28 days. Throw away the used SOLIQUA 100/33 pen after 28 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.

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

For more information, go to www.soliqua100-33.com or call sanofi-aventis at 1-800-633-1610.

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: October 2017

GLX-FPLR-SL-OCT17 Rx Only