Diabetes affects more than 29 million people in the United States—approximately 9% of the US population. In addition, an estimated 86 million US adults (more than 33% of the US population) have prediabetes, a condition that substantially increases the risk for diabetes. Based on the current trends and the aging of the US population in the next few decades, the prevalence of diabetes is projected to increase to 1 in 3 adults by 2050. However, appropriate intervention and management of diabetes can help reduce its rising prevalence.

Type 2 diabetes accounts for 90% to 95% of all cases of diabetes and is characterized by insulin resistance and gradual decline in the ability of the pancreas to produce insulin. Type 1 diabetes accounts for 5% of all cases of diabetes, and is characterized by the destruction of pancreatic beta cells and the insufficiency or the absence of insulin production by the pancreas.

Diabetes was the seventh leading cause of death in the United States in 2013, and is a major cause of stroke, heart disease, kidney failure, blindness, and other serious conditions. Furthermore, diabetes is associated with microvascular, macrovascular, and neuropathic complications that can be disabling, life-threatening, and can have a profound impact on a patient’s health and quality of life.

In the United States, the annual healthcare costs attributed to diabetes totaled $245 billion in 2012, including $176 billion in direct medical costs and $69 billion in indirect costs (ie, absenteeism, reduced/lost productivity, and disability). Overall, the medical costs for patients with diabetes are 2.3 times higher than the costs for individuals without diabetes, with more than 20% of all US healthcare dollars spent on diabetes care.

Effective diabetes management includes lifestyle changes and self-management strategies; appropriate patient education; reducing the risk for weight gain and hypoglycemia; and targeting the patient’s glycated hemoglobin (HbA1c) goal based on several patient factors, including age, comorbid conditions, disease duration, and adherence. Patients with diabetes require ongoing monitoring to evaluate the effectiveness of their therapies toward achieving stable glycemic control.

Improvements in glycemic control are associated with improved outcomes for patients with type 1 or type 2 diabetes. Effective glycemic control reduces the risk for diabetes-related microvascular complications, including diabetic neuropathy, diabetic kidney disease, and retinopathy. However, a 2013 study estimated that 33% to 49% of patients with diabetes do not achieve glycemic control.

Pharmacologic therapies for type 2 diabetes include metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 inhibitors, insulin, and insulin analogs.

For patients with type 2 diabetes who are not achieving their target HbA1c levels despite the addition of basal insulin, the American Diabetes Association recommends advancing to a combination injectable therapy to cover postprandial glucose excursions, with options including the addition of a GLP-1 receptor agonist or a mealtime insulin (ie, a rapid-acting insulin analog that is administered immediately before eating).

New Once-Daily Combination FDA Approved for Type 2 Diabetes

On November 21, 2016, the US Food and Drug Administration (FDA) approved Soliqua 100/33 (insulin glargine [Lantus] 100 units/mL and lixisenatide [Adlyxin] 33 mcg/mL; sanofi-aventis), as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes that is inadequately controlled with basal insulin (<60 units daily) or lixisenatide.

Insulin glargine, the first once-daily, long-acting insulin analog, was initially approved by the FDA in 2000 to improve glycemic control in adult and pediatric patients with type 1 diabetes and in adults with type 2 diabetes; it has a prolonged duration of action without a pronounced peak. Lixisenatide, a GLP-1 receptor agonist, received FDA approval in July 2016 as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes.

The safety and efficacy of lixisenatide as monotherapy and in combination with other FDA-approved therapies, including metformin, sulfonylureas, pioglitazone, and basal insulin, were evaluated in clinical studies involving 5400 patients with type 2 diabetes in which lixisenatide was shown to improve HbA1c levels.
HbA1c and Fasting plasma glucose

Source: Soliqua 100/33 (insulin glargine and lixisenatide injection) prescribing information; November 2016.

### Table 1: Insulin Glargine plus Lixisenatide General Dosing Recommendations

<table>
<thead>
<tr>
<th>Efficacy outcomes</th>
<th>Insulin glargine 100 units/mL plus lixisenatide (N = 365)</th>
<th>Insulin glargine 100 units/mL (N = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded treatment run-in phase, %</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>End of study, mean, %</td>
<td>6.9</td>
<td>7.5</td>
</tr>
<tr>
<td>LS change from baseline, mean, %</td>
<td>–1.1</td>
<td>–0.6</td>
</tr>
<tr>
<td>Patients reaching HbA1c &lt;7% at week 30, %</td>
<td>201 (55.1)</td>
<td>108 (29.6)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean, mg/dL</td>
<td>132.3</td>
<td>132.0</td>
</tr>
<tr>
<td>LS change from baseline, mean, mg/dL</td>
<td>–5.7</td>
<td>–7.0</td>
</tr>
</tbody>
</table>

*Estimated using an ANCOVA with treatment, randomization strata, and country as fixed factors and baseline HbA1c levels as covariate. Overall, 20 patients in the insulin glargine plus lixisenatide group and 10 patients in the insulin glargine 100 units/mL group had missing HbA1c measurements at week 30; these missing measurements were imputed via multiple imputations with respect to the patient’s baseline HbA1c value.

*The differences in effect observed in the clinical trial may not necessarily reflect the effect in care settings in which an alternative insulin glargine dosage can be used.

**ANCOVA** indicates analysis of covariance; CI, confidence interval; HbA1c, glycated hemoglobin; LS, least square.

Source: Soliqua 100/33 (insulin glargine and lixisenatide injection) prescribing information; November 2016.

### Table 2: Insulin Glargine plus Lixisenatide 100/33 versus Insulin Glargine in Patients with Type 2 Diabetes

- **Mechanism of Action**
  - Insulin glargine plus lixisenatide 100/33 is a combination of insulin glargine 100 units/mL and lixisenatide 33 mcg/mL. Insulin glargine regulates glucose metabolism by stimulating peripheral glucose uptake and inhibiting hepatic glucose production. Lixisenatide, a GLP-1 receptor agonist, is a hormone that helps to normalize blood glucose levels by increasing glucose-dependent insulin release, decreasing glucagon secretion, and slowing gastric emptying.

- **Dosing and Administration**
  - Insulin glargine plus lixisenatide 100/33 is available in a 3-mL prefilled, disposable, single-use pen for subcutaneous injection.
  - The insulin glargine plus lixisenatide pen delivers doses from 15 units to 60 units with each injection. For patients requiring an insulin glargine plus lixisenatide daily dose below 15 units or more than 60 units, an alternative antidiabetic treatment should be used.
  - Before starting treatment with insulin glargine plus lixisenatide, patients should discontinue therapy with basal insulin or lixisenatide. The general dosing recommendations for insulin glargine plus lixisenatide are listed in Table 1.

- **The Pivotal LixiLan-L Clinical Trial**
  - The FDA approval of insulin glargine plus lixisenatide was based on the LixiLan-L clinical trial, a randomized, 30-week, active-controlled, open-label study that included 736 patients with type 2 diabetes. In this insulin-intensification study, the efficacy and safety of insulin glargine plus lixisenatide 100/33 were compared with that of insulin glargine 100 units/mL.
  - Patients with type 2 diabetes received a stable daily dose of 15 units to 40 units of basal insulin, alone or combined with 1 or 2 oral antidiabetic drugs, for at least 6 months. The patients’ mean age was 60 years, and the mean duration of diabetes was approximately 12 years.
  - At the end of a 6-week run-in phase, patients with HbA1c levels between 7% and 10% and fasting plasma glucose levels ≤140 mg/dL who received an insulin glargine dose of 20 units to 50 units (mean, 35 units) were randomized to receive insulin glargine plus lixisenatide 100/33 or insulin glargine 100 units/mL.
  - Insulin glargine plus lixisenatide demonstrated a significant mean reduction in HbA1c levels (–1.1) from baseline compared with insulin glargine (–0.6; Table 2). At the end of the study, the doses of insulin glargine were equivalent between the treatment arms. Furthermore, 55.1% of patients who received insulin glargine plus lixisenatide achieved an HbA1c <7% at week 30 compared with 29.6% of patients who received insulin glargine alone (Table 2).

- **Adverse Reactions**
  - The most common (≥5% incidence) adverse reactions associated with insulin glargine plus lixisenatide therapy were nausea (10%), nasopharyngitis (7%), diarrhea (7%), upper respiratory tract infection (5.5%), and headache.
Hypoglycemia is the most common adverse reaction in patients taking insulin or insulin-containing drugs. Hypoglycemia (severe, 0%-1.1%; documented symptomatic, 25.6%-40%) and allergic reactions (anaphylaxis, 0.2%; allergic reactions, such as anaphylactic reaction, angioedema, and urticaria, 0.4%) have been reported with insulin glargine plus lixisenatide therapy.\textsuperscript{11}

Contraindications
Insulin glargine plus lixisenatide is contraindicated during episodes of hypoglycemia. It is also contraindicated in patients with a hypersensitivity to insulin glargine, lixisenatide, or to any of the drugs’ excipients.\textsuperscript{11}

Drug Interactions
The dose of insulin glargine plus lixisenatide may require adjustment when administered concomitantly with drugs that affect glucose metabolism; the patient’s blood glucose levels should be closely monitored.\textsuperscript{11}

Dose reductions of insulin glargine plus lixisenatide and increased monitoring may be warranted when insulin glargine plus lixisenatide is administered with drugs that increase the risk for hypoglycemia. Conversely, dose increases and more frequent monitoring may be required when insulin glargine plus lixisenatide is coadministered with drugs that decrease the blood glucose-lowering effects of insulin glargine plus lixisenatide.\textsuperscript{11}

Lixisenatide delays gastric emptying, which may affect the absorption of concomitantly administered oral medications.\textsuperscript{11} Oral contraceptives should be taken at least 1 hour before the administration of insulin glargine plus lixisenatide. Antibiotics, acetaminophen, or other medications should be taken at least 1 hour before or 11 hours after the administration of insulin glargine plus lixisenatide.\textsuperscript{11}

Warnings and Precautions
Anaphylaxis and serious hypersensitivity reactions. Anaphylaxis and serious hypersensitivity reactions can occur with either of the components of insulin glargine plus lixisenatide. Patients should be instructed to discontinue treatment if a reaction occurs and to promptly seek medical attention.\textsuperscript{11}

Pancreatitis. Insulin glargine plus lixisenatide has not been studied in patients with a history of pancreatitis. Insulin glargine plus lixisenatide should be discontinued if pancreatitis is suspected; treatment should not be restarted if pancreatitis is confirmed.\textsuperscript{11}

Never share the prefilled pen. The insulin glargine plus lixisenatide prefilled pen should never be shared between patients, even if the needle is changed.\textsuperscript{11}

Hyperglycemia or hypoglycemia with changes in treatment regimen. Changes to the insulin glargine plus lixisenatide treatment regimen may predispose patients to hypoglycemia or to hyperglycemia. Treatment regimen changes should be made cautiously and under close medical supervision; furthermore, the patient’s blood glucose levels should be monitored more frequently.\textsuperscript{11}

Overdose because of medication error. Patients should be instructed to check the label before each injection to avoid accidental mix-ups with insulin-containing drugs. The maximum dose of insulin glargin plus lixisenatide should not be exceeded. Insulin glargine plus lixisenatide should not be used with other GLP-1 receptor agonists.\textsuperscript{11}

Hypoglycemia. Hypoglycemia may be life-threatening. The frequency of glucose monitoring should be increased in patients undergoing changes in insulin dosage, when insulin-containing drugs are coadministered with other glucose-lowering drugs, during changes to meal pattern and/or physical activity, and in patients with renal or hepatic impairment and hypoglycemia unawareness.\textsuperscript{11}

Acute kidney injury. Patients with renal impairment and those with severe gastrointestinal adverse reactions should be monitored for renal function. Insulin glargine plus lixisenatide should not be used in patients with end-stage renal disease.\textsuperscript{11}

Immunogenicity. Some patients may have antibodies to insulin glargine plus lixisenatide. An alternative antidiabetic treatment should be considered if glycemic control worsens or if the patient is unable to achieve targeted glycemic control, or if significant injection-site reactions or allergic reactions occur.\textsuperscript{11}

Hypokalemia. Hypokalemia may be life-threatening. Patients at risk for hypokalemia should be monitored for potassium levels and should receive treatment if indicated.\textsuperscript{11}

Fluid retention and heart failure with thiazolidinediones. Thiazolidinediones can cause dose-related fluid retention, particularly when they are used in combination with insulin-containing drugs. Patients should be monitored for signs and symptoms of heart failure; dosage reduction or the discontinuation of thiazolidinediones should be considered if heart failure occurs.\textsuperscript{11}

Macrovascular outcomes. No clinical studies have shown a reduction of macrovascular risk with insulin glargine plus lixisenatide or with any other antidiabetic drug.\textsuperscript{11}

Use in Specific Populations
Pregnancy. There may be risks to the fetus from exposure to lixisenatide during pregnancy. Insulin glargine plus lixisenatide should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.\textsuperscript{11}

Lactation. The developmental and health benefits of breast-feeding should be considered in addition to the mother’s clinical need for insulin glargine plus lixisenatide.
tide and any potential adverse effects on the breast-fed child from insulin glargine plus lixisenatide.\textsuperscript{11}

\textbf{Geriatric use.} No overall differences were observed in the subgroup analyses of patients aged $\geq 65$ years versus patients aged $\geq 75$ years; however, caution should be exercised when administering insulin glargine plus lixisenatide to geriatric patients to avoid hypoglycemia, which may be difficult to detect in geriatric patients.\textsuperscript{11}

\textbf{Renal and hepatic impairment.} Frequent glucose monitoring and dose adjustment may be necessary in patients with renal or hepatic impairment.\textsuperscript{11}

\textbf{Gastroparesis.} Insulin glargine plus lixisenatide is not recommended in patients with severe gastroparesis.\textsuperscript{11}

\section*{Conclusion}

With the FDA approval of insulin glargine plus lixisenatide 100/33, a new, once-daily treatment option became available for adults with type 2 diabetes that is inadequately controlled with basal insulin (<60 units daily) or with lixisenatide. Insulin glargine plus lixisenatide demonstrated significant mean reductions in HbA\textsubscript{1c} levels compared with insulin glargine alone.

In addition, the proportion of patients who achieved an HbA\textsubscript{1c} $<7\%$ was significantly higher in the insulin glargine plus lixisenatide group versus the insulin glargine group.\textsuperscript{13,16}

Insulin glargine plus lixisenatide 100/33 provides patients with inadequately controlled type 2 diabetes with a titratable, fixed-ratio combination of insulin glargine plus lixisenatide in a single, prefilled injection pen for once-daily dosing. \[
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\section*{References}