Insulin glargine / lixisenatide (Soliqua™) New Drug Update

December 2016

<table>
<thead>
<tr>
<th><strong>Drug Name:</strong></th>
<th>Insulin glargine / lixisenatide</th>
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<tbody>
<tr>
<td><strong>Trade Name (Manufacturer):</strong></td>
<td>Soliqua (Sanofi)</td>
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<tr>
<td><strong>Form:</strong></td>
<td>Subcutaneous injection</td>
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<tr>
<td><strong>Strength:</strong></td>
<td>Insulin glargine 100 units and lixisenatide 33 mcg per mL solution in a 3 mL prefilled multi-dose pen</td>
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<td><strong>FDA Approval:</strong></td>
<td>November 21, 2016</td>
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<td><strong>Market Availability:</strong></td>
<td>Anticipated January 2017</td>
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<tr>
<td><strong>FDA Approval Classification:</strong></td>
<td>Standard Review</td>
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<tr>
<td><strong>Classification:</strong></td>
<td>Specific Therapeutic Class (HIC3): Antihyperglycemics, Insulin, Long Acting-GLP-1 Receptor agonist (C4X)</td>
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**INDICATION**

Soliqua, a fixed-dose combination of insulin glargine (Lantus®) and the GLP-1 agonist, lixisenatide (Adlyxin®) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not controlled with basal insulin (< 60 units) or lixisenatide.

Limitations of use:
- Not for treatment of type 1 diabetes or diabetic ketoacidosis
- Not recommended in combination with other products containing a GLP-1 agonist, including lixisenatide
- Not studied in combination with prandial insulin

**CONTRAINDICATIONS/WARNINGS**

Contraindications include use during episodes of hypoglycemia and use in patients with a hypersensitivity to any component of the product.

Cases of pancreatitis were reported in clinical trials of lixisenatide and post-marketing with other GLP-1 agonists. Insulin glargine/lixisenatide should be discontinued in patients with suspected pancreatitis and therapy should not be restarted if pancreatitis is confirmed. Alternative antidiabetic therapies should be considered in patients with a history of pancreatitis.

Acute kidney injury is possible with GLP-1 receptor agonist therapy. Renal function should be monitored when starting or increasing doses of insulin glargine/lixisenatide and in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Patients may develop antibodies to lixisenatide resulting in worsening glycemic control, failure to achieve targeted glycemic control, significant injection site reactions, and/or allergic reactions. Alternative antidiabetic therapies should be considered if this occurs.
As with other insulin-containing products, insulin glargine/lixisenatide, can lead to hypokalemia. Potassium levels should be monitored in at risk patients.

Studies did not include patients with pre-existing gastroparesis; therefore, initiation of insulin glargine/lixisenatide in patients with severe gastroparesis is not recommended.

Concomitant use with a thiazolidinedione (TZD) can lead to dose-related fluid retention, which can in turn exacerbate heart failure (HF). Patients with HF should be monitored appropriately.

**DRUG INTERACTIONS**

Lixisenatide delays gastric emptying which may impact the absorption of concomitantly administered oral medications. Oral medications that are dependent on achieving threshold concentrations for efficacy, or medications for which a delay in effect is undesirable, should be administered 1 hour before insulin glargine/lixisenatide. In addition, appropriate monitoring should be performed for drugs with a narrow therapeutic index with concomitant use of insulin glargine/lixisenatide.

Oral contraceptives should be taken at least 1 hour before insulin glargine/lixisenatide administration or 11 hours after the dose.

Dose reductions or increases of insulin glargine/lixisenatide may be necessary with concurrent use of medications that affect glucose metabolism.

**COMMON ADVERSE EFFECTS**

The most common adverse event reported in clinical trials with insulin glargine/lixisenatide was hypoglycemia. In 2 clinical trials, severe symptomatic hypoglycemia that required medical assistance was reported in up to 1.1% of patients and symptomatic cases with self-monitoring occurred in approximately 25% and 40% of patients.

Other common adverse reactions occurring in ≥ 5% of patients treated with insulin glargine/lixisenatide include nausea (10%), nasopharyngitis and diarrhea (7% each), upper respiratory tract infection (5.5%), and headache (5%).

Gastrointestinal adverse reaction may occur when initiating insulin glargine/lixisenatide therapy.

Injection site reaction occurred in 1.7% of patients treated with insulin glargine/lixisenatide. As with other subcutaneous (SC) insulins, lipoatrophy or lipohypertrophy can occur at injection sites.

Weight gain has been reported in patients treated with insulin glargine/lixisenatide.

**SPECIAL POPULATIONS**

**Pregnancy**

Data regarding use of lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide during pregnancy including visceral closure and skeletal defects. Lixisenatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of insulin glargine during pregnancy has not been associated with a definite association with major fetal harm or risk of miscarriage.
Pediatrics
Safety and effectiveness in pediatric patients have not been established.

Geriatrics
No overall differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population, but individual sensitivity cannot be ruled out.

Hepatic Impairment
No pharmacokinetic study has been performed in patients with hepatic impairment. Frequent glucose monitoring and dose adjustment may be required.

Renal Impairment
Patients with renal impairment may require more frequent glucose monitoring as this population may have increase circulating levels of insulin. However, no dosage adjustment of lixisenatide is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR]: 30 - 89 mL/min/1.73 m²). Patients with severe renal impairment (eGFR: 15 - 30 mL/min/1.73 m²) exposed to lixisenatide should be closely monitored for the 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 insulin glargine/lixisenatide is not recommended for use in this population.

DOSAGES
Discontinue therapy with lixisenatide or basal insulin prior to starting insulin glargine/lixisenatide

Recommended starting dose of insulin glargine/lixisenatide

- For patients not controlled on lixisenatide or < 30 units basal insulin: 15 units SC once daily (equals 15 units insulin glargine and 5 mcg lixisenatide).
- For patients not controlled on 30 to 60 units of basal insulin: 30 units SC once daily (equals 30 units insulin glargine and 10 mcg lixisenatide).

Administer within 1 hour prior to the first meal of the day.

Dosage can be titrated in 2 to 4 unit increments on a weekly basis as-needed. Maximum dose is 60 units.

Prefilled pen delivers from 15 to 60 units in a single injection. In patients who require < 15 units or > 60 units, an alternative antidiabetic product should be prescribed.

The product labeling provides a table with the units insulin glargine and mcg of lixisenatide in each dose of the combination product.

If a dose is missed, therapy should be resumed with the next scheduled dose at the prescribed dosage.

Do not split the dose or mix with other insulins.
**CLINICAL TRIALS**

A literature search was conducted using “lixisenatide, insulin glargine, iGlarLixi, LixiLan.”

A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group study enrolled 736 patients with type 2 diabetes who had been treated with stable doses of basal insulin (15 to 40 units) for at least 6 months with or without oral antidiabetic drugs (OADs). At screening HbA1c was between 7.5% and 10%. Patients were switched to or remained on insulin glargine U-100 during a 6-week run-in period. 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, were randomized to either combination insulin glargine/lixisenatide or insulin glargine U-100. Dosage was titrated to achieve a fasting plasma glucose (FPG) < 100 mg/dL. Maximum insulin glargine dose allowed in either group was 60 units. Target FPG was achieved in 33% of patients in both groups at 30 weeks. At 30 weeks, there was a statistically greater change in HbA1c from baseline for the combination product compared to insulin glargine (mean difference -0.5 [95% confidence interval -0.63, -0.4]). The trial was designed to show the contribution of the GLP-1 component to glycemic lowering and the dosing algorithm was selected to isolate the effect of the GLP-1 component. At week 30, the doses of insulin glargine were the same in both groups (mean 46.7 units). More patients on the combination product achieved HbA1c <7.0% (55%) compared with 30% on insulin glargine. Mean body weight decreased by 0.7 kg with the combination and increased by 0.7 kg with insulin glargine (p<0.0001). The incidence of documented symptomatic hypoglycemia (≤70 mg/dL) was similar in both groups. Mild gastrointestinal adverse effects were very low but more frequent with the combination product.

Efficacy and safety of combination insulin glargine/lixisenatide was compared to the individual components in 1,170 patients with type 2 diabetes inadequately controlled on metformin, with or without a second oral antidiabetic agent. After a 4-week run-in to optimize metformin and stop other oral antidiabetic drugs patients were randomized to open-label once-daily insulin glargine/lixisenatide, insulin glargine, or lixisenatide. Doses in both insulin-containing groups were titrated based on FPG <100 mg/dL to a maximum of 60 units/day. The lixisenatide group received a maximum of 20 mcg once daily. At 30 weeks, greater reductions in HbA1c from baseline were reported with the combination compared with either component alone (-1.6%, -1.3%, -0.9%, respectively). More patients achieved HbA1c <7% with the combination (74%) versus insulin glargine (59%) or lixisenatide (33%) (p<0.0001 for all). Mean change in body weight with the combination was -0.3 kg, lixisenatide -2.3 kg, and insulin glargine +1.1 kg, differences were significant. The incidence of symptomatic hypoglycemia (≤70 mg/dL) was similar with the combination and insulin glargine groups (1.4 and 1.2 events/patient-year, respectively) and lower for the lixisenatide group (0.3 events/patient-year). In addition, the combination improved postprandial glycemic control compared to insulin glargine.

**OTHER DRUGS USED FOR CONDITION**

According to the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2016 Comprehensive Type 2 Diabetes Management Algorithm, treatment recommendations include metformin, GLP-1 receptor agonists, dipeptidyl peptase-4 inhibitors, sodium glucose co-transporter 2 inhibitors, thiazolidinediones, insulin, colesevelam, bromocriptine, sulfonylureas, and alpha glucosidase inhibitors.
PLACE IN THERAPY

In patients with T2DM, dual- and triple-therapy is appropriate when HbA1c is 7.5% or greater. Insulin glargine/lixisenatide targets both FPG and postprandial glucose. The combination product led to greater reductions in HbA1c as compared to either component alone (mean difference -0.3% versus insulin glargine, -0.7% lixisenatide). It is an option for patients who are not controlled with basal insulin (< 60 units) or lixisenatide.

The ELIXA study reported that lixisenatide therapy had a neutral effect on cardiovascular outcomes when compared to placebo (ELIXA).6 While the GLP-1 agonist, liraglutide, a component of the recently approved fixed-dose combination insulin degludec/liraglutide (Xultophy®; Novo Nordisk) has clinical trial data from the LEADER trial demonstrating positive cardiovascular outcomes.7

SUGGESTED UTILIZATION MANAGEMENT

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<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Hypoglycemics, Incretin Mimetics/Enhancers</th>
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<tbody>
<tr>
<td><strong>Clinical Edit</strong></td>
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<tr>
<td></td>
<td>▪ Diagnosis of type 2 diabetes mellitus</td>
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<td></td>
<td>▪ Trial and failure of lixisenatide or</td>
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<tr>
<td></td>
<td>basal insulin separately</td>
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<tr>
<td></td>
<td>▪ If non-preferred, trial and failure of</td>
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<td>preferred GLP-1 receptor agonists and</td>
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<td>preferred long-acting insulin</td>
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<td><strong>Quantity Limit</strong></td>
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<tr>
<td><strong>Duration of Approval</strong></td>
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<tr>
<td><strong>Drug to Disease Hard Edit</strong></td>
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REFERENCES