Lixisenatide (Adlyxin®) New Drug Update

August 2016

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>lixisenatide</th>
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<tbody>
<tr>
<td>Trade Name (Manufacturer):</td>
<td>Adlyxin (Sanofi)</td>
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<tr>
<td>Form:</td>
<td>Injection</td>
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<tr>
<td>Strength:</td>
<td>50 mcg/mL, 100 mcg/mL solution in 3 mL prefilled pen</td>
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<tr>
<td>FDA Approval:</td>
<td>July 27, 2016</td>
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<td>Market Availability:</td>
<td>Anticipated December 2016</td>
</tr>
<tr>
<td>FDA Approval Classification:</td>
<td>Standard Review</td>
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<tr>
<td>Classification:</td>
<td>Specific Therapeutic Class (HIC3): Pending</td>
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INDICATION

Lixisenatide is 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 (T2DM).

CONTRAINDICATIONS/WARNINGS

Lixisenatide is contraindicated in patients with a hypersensitivity to the active ingredient or any of its components.

Anaphylaxis and serious hypersensitivity reactions have occurred with the use of lixisenatide. Lixisenatide should be discontinued in patients who experience an anaphylaxis/hypersensitivity reaction and immediate medical advice should be sought.

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.

Concomitant use of a sulfonylurea or basal insulin with lixisenatide can increase the risk for hypoglycemia. When lixisenatide is used along with a sulfonylurea or basal insulin, lowering the dose of the sulfonylurea or basal insulin should be considered.

Acute kidney injury is possible with GLP-1 receptor agonist therapy. Renal function should be monitored when starting or increasing doses of 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.

Studies did not include patients with pre-existing gastroparesis; therefore initiation of lixisenatide in patients with severe gastroparesis is not recommended.
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 lixisenatide. In addition, appropriate monitoring should be performed for drugs with a narrow therapeutic index with concomitant use of lixisenatide.

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

COMMON ADVERSE EFFECTS

The most common adverse reactions occurring in ≥ 5% of patients treated with lixisenatide and more frequently compared to placebo include nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia.

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.

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 acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.

Renal Impairment

No dosage adjustment 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 lixisenatide is not recommended for use in this population.
DOSAGES

The starting dose of lixisenatide is 10 mcg subcutaneously (in the abdomen, thigh or upper arm) once daily for 14 days. Starting on day 15, the dose should be increased to the maintenance dose of 20 mcg once daily. The dose should be administered within 1 hour before the first meal of the day and the injection site should be rotated.

CLINICAL TRIALS

A literature search was conducted using “lixisenatide.”

GetGoal-X: The GetGoal-X trial was a randomized, open-label, parallel-group, multicenter, non-inferiority study assessing the HbA1c change of lixisenatide once daily versus exenatide twice daily in a total of 634 adult patients with T2DM inadequately controlled with metformin. Patients were randomized to receive either lixisenatide 20 mcg once daily (n = 318) or exenatide 10 mcg twice daily (n = 316) for 24-weeks. The primary objective was a noninferiority assessment of lixisenatide versus exenatide in HbA1c change from baseline to week 24. Lixisenatide once daily achieved the primary efficacy objective of noninferiority to exenatide twice daily in terms of HbA1c reduction from baseline to week 24. The least squares (LS) mean change difference between the 2 groups was 0.17% (95% confidence interval, 0.033 – 0.297), meeting a predefined noninferiority margin of 0.4%. Lixisenatide once daily and exenatide twice daily provided comparable reductions in fasting plasma glucose (LS mean change difference between the two groups was 0.23 mmol/L [4.14 mg/dL; 95% CI, 20.052 - 0.522]). Furthermore, body weight was decreased from baseline for patients receiving each agent (LS mean change difference between the 2 groups was 1.02 kg [95%CI, 0.456 – 1.581]). The most common adverse events in both groups were gastrointestinal in nature, which occurred less frequently in the lixisenatide group versus the exenatide group (43.1% versus 50.6%, respectively). Symptomatic hypoglycemia also occurred less frequently in the lixisenatide group versus the exenatide group (2.5% versus 7.9%, respectively).

ELIXA: The ELIXA trial was a randomized, multicenter, double-blind, placebo-controlled trial designed to assess the effects of lixisenatide on cardiovascular morbidity and mortality. The trial included 6,068 patients with T2DM who experienced an acute coronary event within the last 180 days before screening. Patients were excluded who were < 30 years of age, had a percutaneous intervention within the previous 15 days, a coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, and eGFR < 30 ml/min/1.73 m², a glycated hemoglobin level of less than 5.5% or more than 11%, or an inability to provide written informed consent. Eligible consenting patients were randomly assigned to a once-daily subcutaneous injection of lixisenatide (starting at 10 mcg daily and increased to 20 mcg daily after the first 2 weeks, at the discretion of the investigators) or volume-matched placebo. The primary end point in the time-to-event analysis was a composite of the first occurrence of any of the following: death from cardiovascular causes, nonfatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. The primary end point occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group. The hazard ratio for the primary end point in the lixisenatide group as compared with the placebo group was 1.02 (95% confidence interval [CI], 0.89 to 1.17); the upper boundary of the 95% confidence interval excluded 1.3 but not 1.0, which showed the noninferiority of lixisenatide to placebo (p<0.001) but not superiority (p=0.81).
**OTHER DRUGS USED FOR CONDITION**

According to 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 (albiglutide [Tanzeum®], dulaglutide [Trulicity®], exenatide [Bydureon®, Byetta®], liraglutide [Victoza®]), dipeptidyl peptase-4 inhibitors (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], sitagliptin [Januvia®]), sodium glucose co-transporter 2 inhibitors (canagliflozin [Invokana®], dapagliflozin [Farxiga®], empagliflozin [Jardiance®]), thiazolidinediones (pioglitazone [Actos®], rosiglitazone [Avandia®]), insulin, colesevelam, bromocriptine, sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide), and alpha glucosidase inhibitors (acarbose, miglitol). 4

**PLACE IN THERAPY**

The GLP-1 receptor agonists have robust A1C-lowering properties, are usually associated with weight loss, carry a low risk of hypoglycemia when used alone or in combination with metformin, and reduce fluctuations in both fasting and post-prandial glucose levels. The AACE/ACE 2016 Comprehensive Type 2 Diabetes Management Algorithm lists GLP-1 receptor agonists as an acceptable alternative to metformin as initial therapy for patients with recent-onset T2DM or mild hyperglycemia (HbA1c <7.5%), or as combination therapy with metformin for patients with HbA1c >7.5%. 5 Although not listed in the AACE/ACE algorithm, lixisenatide can be considered a possible treatment option in patients with T2DM because of clinical trial data demonstrating non-inferiority to exenatide. Clinical trial data assessing cardiovascular outcomes showed the effects of lixisenatide therapy were neutral when compared to placebo (ELIXA) while liraglutide has clinical trial data demonstrating positive effects on cardiovascular outcomes (LEADER). 6

**SUGGESTED UTILIZATION MANAGEMENT**

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<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Hypoglycemics, Incretin Mimetics/Enhancers</th>
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| **Clinical Edit** | • Age ≥ 18 years  
• Diagnosis of type 2 diabetes mellitus  
• Trial and failure of metformin  
• If non-preferred, trial and failure of preferred GLP-1 receptor agonists |
| **Quantity Limit** | 2 pens/28 days |
| **Duration of Approval** | 1 year |
| **Drug to Disease Hard Edit** | n/a |

**REFERENCES**
