**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use ADLYXIN safely and effectively. See full prescribing information for ADLYXIN.**

**ADLYXIN (lixisenatide) injection, for subcutaneous use**
**Initial U.S. Approval: 2016**

**----------INDICATIONS AND USAGE----------**
ADLYXIN 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 (1).

Limitations of Use (1):
- Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not for treatment of type 1 diabetes or diabetic ketoacidosis.
- Has not been studied in combination with short acting insulin.
- Has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

**----------DOSAGE AND ADMINISTRATION----------**
- Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily (2.1).
- Administer once daily within one hour before the first meal of the day (2.2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2.2).

**----------DOSAGE FORMS AND STRENGTHS----------**
- Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose) (3).
- Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose) (3).

**----------CONTRAINDICATIONS----------**
Hypersensitivity to ADLYXIN or any product components. Hypersensitivity reactions including anaphylaxis have occurred with ADLYXIN (4).

**----------WARNINGS AND PRECAUTIONS----------**
- Anaphylaxis and Serious Hypersensitivity Reactions: Discontinue ADLYXIN and promptly seek medical advice (5.1).
- Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis (5.2).
- Never share ADLYXIN pen between patients, even if the needle is changed (5.3).
- Hypoglycemia with Concomitant use of Sulfonylurea or Basal Insulin: When ADLYXIN is used with a sulfonylurea or basal insulin, consider lowering the dose of the sulfonylurea or basal insulin to reduce the risk of hypoglycemia. (5.4).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. ADLYXIN is not recommended in patients with end stage renal disease (5.5).
- Immunogenicity: Patients may develop antibodies to 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 (5.6).
- Macrovascular Outcomes: Clinical studies have not shown macrovascular risk reduction with ADLYXIN or any other antidiabetic drug (5.7).

**----------ADVERSE REACTIONS----------**
The most common adverse reactions (≥5%) of patients treated with ADLYXIN are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia (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*.**

**----------DRUG INTERACTIONS----------**
- ADLYXIN delays gastric emptying which may impact absorption of concomitantly administered oral medications. Oral medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered 1 hour before ADLYXIN (7.1, 12.3).
- Oral contraceptives should be taken at least 1 hour before ADLYXIN administration or 11 hours after the dose of ADLYXIN (7.1, 12.3).

**----------USE IN SPECIFIC POPULATIONS----------**
Pregnancy: ADLYXIN 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: 7/2016**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

ADLYXIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use**:**

- ADLYXIN has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.
- ADLYXIN is not a substitute for insulin. ADLYXIN is not indicated for use in patients with type 1 diabetes mellitus or for treatment of diabetic ketoacidosis.
- The concurrent use of ADLYXIN with short acting insulin has not been studied and is not recommended.
- ADLYXIN has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Instructions

- The starting dose of ADLYXIN is 10 mcg subcutaneously once daily for 14 days.
- Increase the dose to the maintenance dose of 20 mcg once daily starting on Day 15.

### 2.2 Important Administration Instructions

- Instruct patients and caregivers on the preparation and use of the pen prior to first use of ADLYXIN. Training should include a practice injection.
- Inspect ADLYXIN visually before use. It should appear clear and colorless. Do not use ADLYXIN if particulate matter or coloration is seen.
- Administer ADLYXIN by subcutaneous injection in the abdomen, thigh or upper arm once daily.
- Rotate injections sites with each dose. Do not use the same site for each injection.
- Instruct patients to administer an injection of ADLYXIN within one hour before the first meal of the day preferably the same meal each day. If a dose is missed, administer ADLYXIN within one hour prior to the next meal.
- Instruct patients to protect the pen from light by keeping it in its original packaging and to discard pen 14 days after its first use.

## 3 DOSAGE FORMS AND STRENGTHS

ADLYXIN is a clear solution for subcutaneous injection available as:

- 50 mcg/mL in 3 mL solution in a green single-patient use prefilled pen (for 14 doses; 10 mcg/dose)

- 100 mcg/mL in 3 mL solution in a burgundy single-patient use prefilled pen (for 14 doses; 20 mcg/dose)

## 4 CONTRAINDICATIONS

ADLYXIN is contraindicated in patients with known hypersensitivity to lixisenatide or to any component of ADLYXIN. Hypersensitivity reactions including anaphylaxis have occurred with ADLYXIN *[see Warnings and Precautions (5.1) and Adverse reactions (6.1)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Anaphylaxis and Serious Hypersensitivity Reactions

In clinical trials of ADLYXIN, there have been cases of anaphylaxis determined to be related to ADLYXIN (frequency of 0.1% or 10 cases per 10,000 patient-years). Other serious hypersensitivity reactions including angioedema also occurred *[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 ADLYXIN. ADLYXIN is contraindicated in patients with known hypersensitivity to lixisenatide *[see Contraindications (4)]*. If a hypersensitivity reaction occurs, the patient should discontinue ADLYXIN and promptly seek medical attention.

### 5.2 Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported postmarketing in patients treated with GLP-1 receptor agonists. In clinical trials of ADLYXIN, there were 21 cases of pancreatitis among ADLYXIN-treated patients and 14 cases in comparator-treated patients (incidence rate of 21 vs. 17 per 10,000 patient-years). ADLYXIN cases were reported as acute pancreatitis (n=3), pancreatitis (n=12), chronic pancreatitis (n=5), and edematous pancreatitis (n=1). Some patients had risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

After initiation of ADLYXIN, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue ADLYXIN and initiate appropriate management. If pancreatitis is confirmed, do not restart ADLYXIN. Consider antidiabetic therapies other than ADLYXIN in patients with a history of pancreatitis.

### 5.3 Never Share ADLYXIN Pen Between Patients

ADLYXIN pens should never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

### 5.4 Hypoglycemia with Concomitant Use of Sulfonylurea or Basal Insulin

Patients receiving ADLYXIN in combination with basal insulin or a sulfonylurea have an increased risk of hypoglycemia. In patients receiving sulfonylurea with or without metformin, 14.5% patients on ADLYXIN reported symptomatic hypoglycemia compared to 10.6% for those on placebo. In patients receiving basal insulin with or without metformin, 28.3% patients on

ADLYXIN reported symptomatic hypoglycemia compared to 23.0% for those on placebo. In patients receiving basal insulin with sulfonylurea, 47.2% patients on ADLYXIN reported symptomatic hypoglycemia compared to 21.6% for those on placebo. Reduction in the dose of sulfonylurea or basal insulin may be necessary. *[see Adverse Reactions (6.1) and Drug Interactions (7.2)]*.

**5.5 Acute Kidney Injury**

Acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis has been reported postmarketing in patients treated with GLP-1 receptor agonists. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

Monitor renal function when initiating or escalating doses of ADLYXIN in patients with renal impairment and in patients reporting severe gastrointestinal reactions. ADLYXIN is not recommended in patients with end stage renal disease *[see Use in Specific Populations (8.6)]*.

**5.6 Immunogenicity**

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

If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, alternative antidiabetic therapy should be considered *[see Adverse Reactions (6.1)]*.

**5.7 Macrovascular Outcomes**

Clinical studies have not shown macrovascular risk reduction with ADLYXIN or any other antidiabetic drug *[see Clinical Studies (14)]*.

**6 ADVERSE REACTIONS**

The following serious reactions are described below or elsewhere in the prescribing information:

- Anaphylaxis and Serious Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Sulfonylurea or Basal Insulin *[see Warnings and Precautions (5.4)]*
- Renal Failure *[see Warnings and Precautions (5.5)]*
- Immunogenicity *[see Warnings and Precautions (5.6)]*

**6.1 Clinical Trials Experience**

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

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from the placebo-controlled trials *[see Clinical Studies (14)]*.

These data reflect exposure of 2869 patients to ADLYXIN and a mean duration of exposure to ADLYXIN of 21.7 weeks. Across the treatment arms, the mean age of patients was 56.1 years, 2.3% were 75 years or older and 48.2% were male. The population in these studies was 63.7% White, 2.6% Black or African American, 32.0% Asian; 18.9% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 8.1%. At baseline, 11.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 $m^2$) in 95.3% of the pooled study populations.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of ADLYXIN in the pool of placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on ADLYXIN than on placebo, and occurred in at least 5% of patients treated with ADLYXIN.

**Table 1: Adverse Reactions Reported in ≥5% of ADLYXIN-Treated Patients with Type 2 Diabetes Mellitus and Occurring More Frequently Compared to Placebo**

| Adverse reaction | Placebo (N=1639) | ADLYXIN (N=2869) |
|---|---|---|
| Nausea | 6% | 25% |
| Vomiting | 2% | 10% |
| Headache | 6% | 9% |
| Diarrhea | 6% | 8% |
| Dizziness | 4% | 7% |

**hypoglycemia is discussed separately*

*Gastrointestinal Adverse Reactions*

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving ADLYXIN than placebo (placebo 18.4%, ADLYXIN 39.7%). More patients receiving ADLYXIN (4.3%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.5%). Investigators graded the severity of gastrointestinal adverse reactions occurring on ADLYXIN as "mild" in 64.2% of cases, "moderate" in 32.3% of cases, or "severe" in 3.5% of cases. The majority of these adverse reactions occurred during the first 3 weeks after starting treatment.

In addition to the reactions in Table 1, the following adverse reactions were reported in >2% of patients and more frequently in ADLYXIN-treated patients than placebo (frequencies listed, respectively, as: placebo; ADLYXIN): dyspepsia (0.2%, 3.2%), constipation (1.8%, 2.8%), abdominal distension (0.9%, 2.2%), abdominal pain upper (0.9%, 2.2%), abdominal pain (1.5%, 2.0%).

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