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

----------RECENT MAJOR CHANGES----------

Warnings and Precautions,
Severe Gastrointestinal Adverse Reactions (5.6) 5/2025
Warnings and Precautions, Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.9) 11/2024

----------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)

----------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 a 3 mL single-patient-use prefilled pen (for 14 doses of 10 mcg per dose). (3)
- Injection: 100 mcg/mL in a 3 mL single-patient-use prefilled pen (for 14 doses of 20 mcg per dose). (3)

----------CONTRAINDICATIONS----------

Severe hypersensitivity to lixisenatide or any component of ADLYXIN. (4)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis and Serious Hypersensitivity Reactions: Discontinue ADLYXIN and promptly seek medical advice. (5.1)
- Acute Pancreatitis: Has been observed in patients treated with GLP-1 receptor agonists, including ADLYXIN. Discontinue if pancreatitis is suspected. (5.2)
- Never share ADLYXIN pen between patients, even if the needle is changed. (5.3)
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary. (5.4)
- Acute Kidney Injury Due to Volume Depletion: Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. ADLYXIN is not recommended in patients with end stage renal disease. (5.5)
- Severe Gastrointestinal Adverse Reactions: Use has been associated with gastrointestinal adverse reactions, sometimes severe. ADLYXIN is not recommended in patients with severe gastroparesis(5.6).
- 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. (5.7)
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. (5.8)
- Pulmonary Aspiration During General Anesthesia or Deep Sedation: Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.9)

----------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: 5/2025

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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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

- The starting dose of ADLYXIN is 10 mcg subcutaneously once daily for 14 days. Initiation with the 10 mcg once daily dosage is intended to reduce the risk of gastrointestinal adverse reactions *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]* and is not effective for glycemic control in adults.
- 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.

3 DOSAGE FORMS AND STRENGTHS

ADLYXIN is a clear and colorless solution available as:

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

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

4 CONTRAINDICATIONS

ADLYXIN is contraindicated in patients with known severe 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 glucagon-like peptide-1 (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 Acute Pancreatitis

Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists *[see Adverse Reactions (6)]*.

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, discontinue ADLYXIN and initiate appropriate management.

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 Insulin Secretagogues or Insulin

Patients receiving ADLYXIN in combination with basal insulin or insulin secretagogue (e.g., sulfonylurea) have an increased risk of hypoglycemia, including severe 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 *[see Adverse Reactions (6.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia *[see Drug Interactions (7.2)]*.

5.5 Acute Kidney Injury Due to Volume Depletion

There have been postmarketing reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with GLP-1 receptor agonists *[see Adverse Reactions (6.3)]*. The majority of the reported events occurred in patients who experienced gastrointestinal reactions leading to dehydration such as nausea, vomiting, or diarrhea *[see Adverse Reactions (6.1)]*. Monitor renal function in patients reporting adverse reactions to ADLYXIN that could lead to volume depletion, especially during dosage initiation and escalation of ADLYXIN.

ADLYXIN is not recommended in patients with end stage renal disease *[see Use in Specific Populations (8.6)]*.

5.6 Severe Gastrointestinal Adverse Reactions

Use of GLP-1 receptor agonists, including ADLYXIN, has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions (6.)]*. ADLYXIN is not recommended in patients with severe gastroparesis.

5.7 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)]*.

5.8 Acute Gallbladder Disease

Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In the ELIXA study *[see Clinical Studies (14.6)]*, cholelithiasis occurred in 0.4% of ADLYXIN-treated patients versus 0.2% in placebo-treated patients and acute cholecystitis in 0.3% of ADLYXIN-treated patients versus 0.2% in placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

5.9 Pulmonary Aspiration During General Anesthesia or Deep Sedation

ADLYXIN delays gastric emptying *[see Clinical Pharmacology (12.1)]*. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking ADLYXIN, including whether modifying preoperative fasting recommendations or temporarily discontinuing ADLYXIN could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ADLYXIN.

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)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury Due to Volume Depletion *[see Warnings and Precautions (5.5)]*

- Severe Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immunogenicity *[see Warnings and Precautions (5.7)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.8)]*
- Pulmonary Aspiration During General Anesthesia or Deep Sedation *[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 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, and 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.

Other Adverse Reactions

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%).

Hypoglycemia

Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying plasma glucose <60 mg/dL or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration if no plasma glucose value was available.

Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia in which the patient required the assistance of another person, associated with a plasma glucose level below 36 mg/dL or, associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration if no plasma glucose was available.

Table 2 summarizes the incidence of symptomatic hypoglycemia and severe hypoglycemia in seven placebo-controlled efficacy/safety studies.

Table 2: Incidence (%) of Symptomatic Hypoglycemia and Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus during the 24-week Main Treatment Period

Background Therapy	Placebo	ADLYXIN
Monotherapy*	**N=122**	**N=239**
Symptomatic (%)	2	2
Severe (%)	0	0
With Metformin	**N=432**	**N=946**
Symptomatic (%)	1	3
Severe (%)	0	0
With Sulfonylurea +/- metformin	**N=377**	**N=656**
Symptomatic (%)	11	15
Severe (%)	0	0.2
With Pioglitazone +/- metformin	**N=161**	**N=323**
Symptomatic (%)	1	3
Severe (%)	0	0
With Basal insulin +/- metformin	**N=213**	**N=374**
Symptomatic (%)	23	28
Severe (%)	0	1
With Basal insulin +/- sulfonylurea	**N=111**	**N=108**
Symptomatic (%)	22	47
Severe (%)	0	0
With Insulin Glargine and metformin +/- thiazolidinedione	**N=223**	**N=223**
Symptomatic (%)	14	22
Severe (%)	0	0.4

* 12-week treatment duration.

Injection site reactions

Injections site reactions (e.g., pain, pruritus, and erythema) were reported more frequently in ADLYXIN-treated patients (4%) than placebo treated patients (2%).

Anaphylaxis and hypersensitivity

In the ADLYXIN 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 ADLYXIN-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 ADLYXIN-treated patients (0.4%) than placebo-treated patient (0.2%).

Pancreatitis

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.

Acute Gallbladder Disease

In the ELIXA study *[see Clinical Studies (14.6)]*, cholelithiasis occurred in 0.4% of ADLYXIN-treated patients versus 0.2% in placebo-treated patients and acute cholecystitis in 0.3% of ADLYXIN-treated patients versus 0.2% in placebo-treated patients.

6.2 Immunogenicity

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 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 (5.7)]*.

Anti-lixisenatide antibody characterization studies have demonstrated the potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon, but the clinical significance of these antibodies is not currently known.

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, the incidence of antibodies to lixisenatide cannot be directly compared with the incidence of antibodies with other products.

6.3 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of ADLYXIN. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: acute pancreatitis, hemorrhagic and necrotizing pancreatitis, ileus

Hepatobiliary: cholecystitis, cholelithiasis requiring cholecystectomy

Neurologic: dysgeusia, dysesthesia

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

Renal: Acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis

Skin and Subcutaneous Tissue: alopecia

7 DRUG INTERACTIONS

7.1 Delayed Gastric Emptying Effects on Oral Medications

ADLYXIN 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 ADLYXIN. If such medications are to be administered with food, patients should be advised to take them with a meal or snack when ADLYXIN is not administered.

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 at least 1 hour before ADLYXIN injection *[see Clinical Pharmacology (12.3)]*.

Patients taking oral contraceptives should be advised to take them at least 1 hour before ADLYXIN administration or at least 11 hours after the dose of ADLYXIN *[see Clinical Pharmacology (12.3)]*.

7.2 Dosage Adjustment of Sulfonylurea or Insulin with Concomitant Use with ADLYXIN

When initiating ADLYXIN, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide during pregnancy. ADLYXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 mcg/day clinical dose, respectively, based on plasma AUC *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pregestational diabetes with a 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 embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal data

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg during organogenesis (gestation day 6 to 17), fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥5 mcg/kg/day, resulting in systemic exposure that is 1-time the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse 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 in 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 ≥5 mcg/kg/day or systemic exposures that are 6-times the 20 mcg/day 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 in 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, 20, or 200 mcg/kg from gestation day

6 through lactation, decreases in maternal body weight, food consumption, 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 mcg/m^2.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ADLYXIN in human milk, the effects on the breastfed infant, or the effects on milk production. However, 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 lixisenatide and any potential adverse effects on the breastfed infant from lixisenatide or from the underlying maternal condition.

Data

Animal data

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.01%) levels of unchanged lixisenatide protein in the gastric contents of weaning offspring.

8.4 Pediatric Use

Safety and effectiveness of ADLYXIN have not been established in pediatric patients.

8.5 Geriatric Use

In clinical studies of ADLYXIN, a total of 1837 (25%) of the patients exposed to the study medication were 65 years of age and over and 288 (4%) were 75 years of age and over. No overall differences were observed in safety or effectiveness between these patients and younger patients, but individual sensitivity cannot be ruled out.

8.6 Renal Impairment

In patients with mild renal impairment (eGFR: 60-89 mL/min/1.73 m^2) no dose adjustment is required *[see Clinical Pharmacology (12.3)]* but close monitoring for ADLYXIN related adverse reactions *[see Adverse Reactions (6.1)]* and for changes in renal function is recommended because a higher incidence of hypoglycemia, nausea and vomiting were observed in these patients.

In a cardiovascular outcome study, 655 (22%) lixisenatide treated patients had moderate renal impairment (eGFR: 30 to less than 60 mL/min/1.73 m^2). No dosing adjustment is recommended in patients with moderate renal impairment *[see Clinical Pharmacology (12.3)]* but close monitoring for ADLYXIN related adverse gastrointestinal reactions *[see Adverse Reactions (6.1)]* and for changes in renal function is recommended because these may lead to dehydration and acute kidney injury in these patients *[see Warnings and Precautions (5.5)]*.

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 m^2) exposed to ADLYXIN in all controlled studies. Lixisenatide exposure was higher in these patients *[see Clinical Pharmacology (12.3)]*. Patients with severe renal impairment exposed to ADLYXIN should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes

in renal function *[see Warnings and Precautions (5.5)]*.

There is no therapeutic experience in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use ADLYXIN in this population *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In case of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Initiate appropriate supportive treatment according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Lixisenatide is a synthetic analogue of human GLP-1 and acts as a GLP-1 receptor agonist. Lixisenatide is a protein containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44) and has a molecular weight of 4.8585 kDa.

ADLYXIN (lixisenatide) injection is a sterile, clear and colorless solution for subcutaneous use. ADLYXIN is supplied as 3 mL single-patient-use prefilled pens. Each mL contains either 50 mcg of lixisenatide (green prefilled pen) or 100 mcg of lixisenatide (burgundy prefilled pen) and the inactive ingredients: glycerol 85% (54 mg), metacresol (8.1 mg), methionine (9.0 mg), sodium acetate trihydrate (10.5 mg), and Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. The pH is approximately 4.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lixisenatide is a GLP-1 receptor agonist. Lixisenatide increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.

12.2 Pharmacodynamics

In a clinical pharmacology study in adults with type 2 diabetes mellitus, ADLYXIN reduced fasting plasma glucose and postprandial blood glucose $AUC_{0\text{-}300min}$ 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.

Glucagon secretion

Treatment with ADLYXIN 20 mcg once daily reduced postprandial glucagon levels ($AUC_{0\text{-}300min}$) compared to placebo by -15.6 h·pmol/L after a standardized test meal in patients with type 2 diabetes.

Cardiac electrophysiology (QTc)

At a dose 1.5 times the recommended dose, ADLYXIN does not prolong the QTc interval to any clinically relevant extent.

Heart Rate

No increase in mean heart rate was seen in placebo-controlled studies.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration in patients with type 2 diabetes, the median t_{max} is 1 to 3.5 hours. There are no clinically relevant differences in the rate of absorption when lixisenatide is administered subcutaneously in the abdomen, thigh, or arm.

Distribution

The apparent volume of distribution after subcutaneous administration of lixisenatide (Vz/F) is approximately 100 L.

Elimination

Metabolism and Elimination

Lixisenatide is presumed to be eliminated through glomerular filtration, and proteolytic degradation.

After multiple dose administration in patients with type 2 diabetes, mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h.

Specific Populations

Effects of Age, Body weight, Gender, and Race

Age, body weight, gender, and race were not observed to meaningfully affect the pharmacokinetics of lixisenatide in population PK analyses *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment

Compared to healthy subjects (Creatinine Clearance using Cockcroft-Gault [CLcr] greater than or equal to 90 mL/min [N=4]), plasma C_{max} of lixisenatide was increased by approximately 60%, 42%, and 83% in patients with mild (CLcr 60-89 mL/min [N=9]), moderate (CLcr 30-59 mL/min [N=11]), and severe (CLcr 15-29 mL/min [N=8]) renal impairment. Plasma AUC was increased by approximately 34%, 69%, and 124% with mild, moderate, and severe renal impairment, respectively *[see Use in Specific Populations (8.6)]*.

Patients with 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.

Drug Interaction Studies

Acetaminophen

ADLYXIN 10 mcg did not change the overall exposure (AUC) of acetaminophen following administration of a single dose of acetaminophen 1000 mg, whether before or after ADLYXIN. No effects on acetaminophen C_{max} and t_{max} were observed when acetaminophen was administered 1 hour before ADLYXIN. When administered 1 or 4 hours after 10 mcg of ADLYXIN, C_{max} of acetaminophen was decreased by 29% and 31%, respectively, and median t_{max} was delayed by 2.0 and 1.75 hours, respectively.

Oral contraceptives

Administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after 10 mcg of ADLYXIN, did not change C_{max}, AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel.

Administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour or 4 hours after 10 mcg of ADLYXIN did not affect the overall exposure (AUC) and mean terminal half-life ($t_{1/2}$) of ethinylestradiol and levonorgestrel. However, C_{max} of ethinylestradiol was decreased by 52% and 39%, respectively, and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively, and median t_{max} was delayed by 1 to 3 hours *[see Drug Interactions (7.1)]*.

Atorvastatin

When ADLYXIN 20 mcg and atorvastatin 40 mg were coadministered in the morning for 6 days, the overall exposure (AUC) of atorvastatin was not affected, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours. No such increase for t_{max} was observed when atorvastatin was administered in the evening and ADLYXIN in the morning but the AUC and C_{max} of atorvastatin were increased by 27% and 66%, respectively.

Warfarin and other coumarin derivatives

After concomitant administration of warfarin 25 mg with repeated dosing of ADLYXIN 20 mcg, there were no effects on AUC or INR (International Normalized Ratio) while C_{max} was reduced by 19% and t_{max} was delayed by 7 hours *[see Drug Interactions (7.1)]*.

Digoxin

After concomitant administration of ADLYXIN 20 mcg and digoxin 0.25 mg at steady state, the AUC of digoxin was not affected. The t_{max} of digoxin was delayed by 1.5 hour and the C_{max} was reduced by 26% *[see Drug Interactions (7.1)]*.

Ramipril

After concomitant administration of ADLYXIN 20 mcg and ramipril 5 mg during 6 days, the AUC of ramipril was increased by 21% while the C_{max} was decreased by 63%. The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2.5 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 1,000 mcg/kg. A statistically significant increase in thyroid C-cell adenomas was observed in male mice at 2,000 mcg/kg/day, resulting in systemic exposures that are >180-times the human exposure achieved at 20 mcg/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 mcg/day based on plasma AUC. A numerical increase in thyroid C-cell carcinomas was observed in rats at ≥400 mcg/kg/day, resulting in systemic exposures that are >56-times the human exposure

achieved at 20 mcg/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 micronucleus).

Impairment of Fertility

Studies in which male and female rats received twice daily subcutaneous doses of 2, 29, or 414 mcg/kg/dose 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/dose, which is approximately 400-times the clinical dose at 20 mcg/day based on mcg/m^2.

14 CLINICAL STUDIES

ADLYXIN has been studied as monotherapy, in combination with oral antidiabetic medications, and in combination with basal insulin (with or without oral antidiabetic medications). The efficacy of ADLYXIN was compared with placebo, exenatide, and insulin glulisine.

In patients with type 2 diabetes, ADLYXIN produced reductions from baseline in HbA1c compared to placebo.

14.1 Monotherapy

In a 12-week double blind study, 241 patients with type 2 diabetes inadequately controlled on diet and exercise were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 53.9 years, and the mean duration of type 2 diabetes mellitus was 2.5 years; 51.0% were male, 72.6% were White, 2.5% were Black or African American, 22.0% were Hispanic, and 3.7% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 32 kg/m^2.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 12 (see Table 3). The adjusted mean change in weight from baseline did not differ significantly between ADLYXIN (-1.9 kg) and placebo (-2.0 kg).

Table 3: Placebo-Controlled Study (12-week treatment period results) – Intent-To-Treat (ITT) Population

	Placebo (N=122)	**ADLYXIN 20 mcg (N=119)**
HbA_{1c} (%)		
Baseline (mean)	8.07	8.07
LS mean change from baseline*	-0.18	-0.83
Difference from placebo (95% CI)		-0.65 (-0.903, -0.399) (p<0.0001)
Patients (%) achieving HbA_{1c} <7.0%†	24	44
Fasting plasma glucose (FPG) (mg/dL)		
Baseline (mean)	160.39	162.77
LS mean change from baseline*	1.46	-15.84
Body weight (kg)		
Baseline (mean)	86.08	86.50

LS mean change from baseline*	-2.03	-1.94

ITT population = all randomized patients.
10% of patients in ADLYXIN and 10% in the placebo had missing HbA1c data at Week 12 in the ITT population.
* Using multiple imputation with respect to jump to placebo for missing data at Week 12 in the ADLYXIN group.
† Patients with missing HbA1c value at Week 12 were considered nonresponders.

14.2 Add-on Combination Therapy to Metformin (Alone or in Combination with Sulfonylurea)

In a 24-week study, 323 patients with type 2 diabetes inadequately controlled on diet, exercise, and metformin were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 56.7 years, and the mean duration of type 2 diabetes mellitus was 5.9 years; 44.6% were male, 90.1% were White, 0.6% were Black or African American, 27.9% were Hispanic, and 1.2% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 33 kg/m^2. The mean dose of metformin was 1955 mg per day.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 4).

Table 4: Placebo-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with Metformin (24-week results) – ITT Population

Background Therapy	**with Metformin***	
	Placebo (N=162)	**ADLYXIN 20 mcg (N=161)**
HbA_{1c} (%)		
Baseline (mean)	8.03	7.99
LS mean change from baseline†	-0.26	-0.72
Difference from placebo (95% CI)		-0.46 (-0.640, -0.279) (p<0.0001)
Patients (%) achieving HbA_{1c} <7.0%‡	22	44
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline (mean)	170.32	172.23
LS mean change from baseline†	-7.25	-16.88
Difference from placebo (95% CI)		-9.64 (-16.306, -2.970) (p=0.0046)
Body weight (kg)		
Baseline (mean)	87.87	90.21
LS mean change from baseline†	-1.71	-2.70
Difference from placebo (95% CI)		-1.00 (-1.706, -0.286) (p=0.006)

ITT population = all randomized patients.
* 11% of patients in ADLYXIN 20 mcg and 6% in the placebo had missing HbA1c data at Week 24 in the ITT population.
† Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.
‡ Patients with missing HbA1c value at Week 24 were considered nonresponders.

In a 24-week study, 391 Asian patients with type 2 diabetes inadequately controlled on diet, exercise, and metformin with or without a sulfonylurea were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 54.8 years, and mean duration of type 2 diabetes mellitus was 6.6 years. 49.1% were male. All patients were Asian. 2.8% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 27 kg/m^2. The mean dose of metformin was 1368 mg per day and 44.8% of patients were on a sulfonylurea.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 5).

Table 5: Placebo-Controlled Study in Asian Patients with Type 2 Diabetes Mellitus in Combination with Metformin with or without Sulfonylurea (24-week results) – ITT Population

Background Therapy	with Metformin +/- Sulfonylurea*	
	Placebo (N=195)	ADLYXIN 20 mcg (N=196)
HbA_{1c} (%)		
Baseline (mean)	7.85	7.95
LS mean change from baseline†	-0.57	-0.84
Difference from placebo (95% CI)		-0.27 (-0.447, -0.090) (p=0.0032)
Patients (%) achieving HbA_{1c} <7.0%‡	37	49
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline (mean)	157.47	159.26
LS mean change from baseline†	-7.05	-13.39
Body weight (kg)		
Baseline (mean)	72.74	73.18
LS mean change from baseline†	-1.12	-1.36

ITT population = all randomized patients.
* 7% of patients in ADLYXIN and 6% in the placebo had missing HbA1c data at Week 24 in the ITT population.
† Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.
‡ Patients with missing HbA1c value at Week 24 were considered nonresponders.

In a 24-week open-label study, 634 patients with type 2 diabetes inadequately controlled on diet, exercise and metformin were randomized to ADLYXIN 20 mcg once daily or exenatide 10 mcg twice daily. The mean age of the study population was 57.4 years, and mean duration of type 2 diabetes mellitus was 6.8 year; 53.3% were male, 92.7% were White, 2.8% were Black or African American, 26.8% were Hispanic, and 1.7% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 34 kg/m^2. The mean dose of metformin was 2039 mg per day.

ADLYXIN 20 mcg once daily met the prespecified noninferiority margin of 0.4% versus exenatide 10 mg BID for the difference in HbA1c reduction from baseline (see Table 6). However in this study, ADLYXIN provided less HbA1c reduction than exenatide 10 mg BID and the difference was statistically significant (p=0.0175).

Table 6: Active-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with Metformin (24-week treatment period results) – ITT Population

	ADLYXIN (N=318)	Exenatide BID (N=316)
HbA1c (%)		
Baseline (mean)	7.95	7.97
LS Mean change from baseline*	-0.73	-0.90
LS mean difference vs Exenatide BID*	0.17	
95% CI	(0.030 to 0.314) (p=0.0175)	
Patients (%) achieving HbA_{1c} <7.0%†	43.1	45.6
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline	174.24	173.88

	ADLYXIN (N=318)	Exenatide BID (N=316)
LS Mean change from baseline	-19.79	-24.19
Body weight (kg)		
Baseline	94.01	96.09
LS Mean change from baseline	-2.74	-3.72

ITT population = all randomized patients.
14% of patients in ADLYXIN and 14% in exenatide had missing HbA1c data at Week 24 in the ITT population.
* Using multiple imputation with respect to use the baseline value for missing data at Week 24 in each group.
† Patients with missing HbA1c value at Week 24 were considered nonresponders.

14.3 Add-on Combination Therapy to a Sulfonylurea (Alone or in Combination with Metformin)

In a 24-week study, 859 patients with type 2 diabetes inadequately controlled with diet, exercise and a sulfonylurea with or without metformin were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 57.2 years, and mean duration of type 2 diabetes mellitus was 9.3 years; 50.5% were male, 52.2% were White, 3.0% were Black or African American, 2.7% were Hispanic, and 4.7% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 30 kg/m^2. The two most common sulfonylureas used were glimepiride and glibenclamide and the mean dose of these drugs at baseline were 5.1 mg and 12.9 mg, respectively, and 84.4% of patients were on metformin.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 7).

Table 7: Placebo-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with a Sulfonylurea (24-week results) – ITT Population

Background Therapy	with Sulfonylurea +/- Metformin*	
	Placebo (N=286)	ADLYXIN 20 mcg (N=573)
HbA_{1c} (%)		
Baseline (mean)	8.21	8.28
LS mean change from baseline†	-0.18	-0.77
Difference from placebo (95% CI)		-0.58 (-0.715, -0.453) (p<0.0001)
Patients (%) achieving HbA_{1c} <7.0%‡	13	33
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline (mean)	167.47	174.24
LS mean change from baseline†	-10.36	-17.09
Difference from placebo (95% CI)		-6.73 (-11.946, -1.518) (p=0.0114)
Body weight (kg)		
Baseline (mean)	84.34	82.34
LS mean change from baseline†	-0.83	-1.63
Difference from placebo (95% CI)		-0.80 (-1.244, -0.349) (p=0.0005)

ITT population = all randomized patients.
* 13% of patients in ADLYXIN and 13% in the placebo had missing HbA1c data at Week 24 in the ITT population.
† Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.
‡ Patients with missing HbA1c value at Week 24 were considered nonresponders.

14.4 Add-on Treatment to Pioglitazone (Alone or in Combination with Metformin)

In a 24-week study, 484 patients with type 2 diabetes with inadequately controlled with diet, exercise and pioglitazone with or without metformin were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 55.8 years, and mean duration of type 2 diabetes mellitus was 8.1 years; 52.5% were male, 83.7% were White, 4.8% were Black or African American, 26.4% were Hispanic, and 4.1% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 34 kg/m^2. The mean dose of pioglitazone was 33.6 mg per day and 81.0% of patients were on metformin.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 8).

Table 8: Placebo-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with Pioglitazone (24-week results) – ITT Population

Background Therapy	Pioglitazone +/- Metformin*	
	Placebo (N=161)	**ADLYXIN 20 mcg (N=323)**
HbA_{1c} (%)		
Baseline (mean)	8.06	8.08
LS mean change from baseline†	-0.43	-0.91
Difference from placebo (95% CI)		-0.48 (-0.647, -0.318) (p<0.0001)
Patients (%) achieving HbA_{1c} <7.0%‡	25	49
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline (mean)	164.49	164.16
LS mean change from baseline†	-14.12	-24.56
Difference from placebo (95% CI)		-10.45 (-16.580, -4.315) (p=0.0008)
Body weight (kg)		
Baseline (mean)	96.74	92.93
LS mean change from baseline†	0.26	-0.11

ITT population = all randomized patients.
* 9% of patients in ADLYXIN and 12% in the placebo had missing HbA1c data at Week 24 in the ITT population.
† Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.
‡ Patients with missing HbA1c value at Week 24 were considered nonresponders.

14.5 Add-on to Basal Insulin (Alone or in Combination with Oral Antidiabetics)

In a 24-week study, 496 patients with type 2 diabetes inadequately controlled on diet, exercise and basal insulin with or without metformin were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 57.2 years, and mean duration of type 2 diabetes mellitus was 12.46 years; 46.0% were male, 77.6% were White, 4.0% were Black or African American, 27.0% were Hispanic, and 3.2% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 32 kg/m^2. At baseline, the mean basal insulin dose was 54.9 units and 79.2% of individuals were receiving metformin.

In another 24-week study, 311 Asian patients with type 2 diabetes inadequately controlled on diet, exercise and basal insulin with or without a sulfonylurea were randomized to ADLYXIN 20 mcg once daily or to placebo. The mean age of the study population was 58.4 years, and mean duration of type 2 diabetes mellitus was 13.92 years; 47.9% were male, all patients were Asian, and 15.8% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 25 kg/m^2. At baseline, the mean basal insulin dose was 24.2 units and 70.4% of individuals were receiving a sulfonylurea.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 9) in both studies.

Table 9: Placebo-Controlled Studies in Patients with Type 2 Diabetes Mellitus in Combination with a Basal Insulin (24-week treatment period results) – ITT Population

Background Therapy	with Basal Insulin +/- Metformin*		with Basal Insulin +/- Sulfonylurea†	
	Placebo (N=167)	ADLYXIN 20 mcg (N=329)	Placebo (N=157)	ADLYXIN 20 mcg (N=154)
HbA_{1c} (%)				
Baseline (mean)	8.37	8.42	8.52	8.54
LS mean change from baseline‡	-0.34	-0.71	0.07	-0.70
Difference from placebo (95% CI)		-0.36 (-0.557, -0.170) (p=0.0002)		-0.76 (-1.005, -0.516) (p<0.0001)
Patients (%) achieving HbA_{1c} <7.0%§	11	25	6	33
Fasting Plasma Glucose (FPG) (mg/dL)				
Baseline (mean)	144.94	146.44	139.69	138.25
LS mean change from baseline‡	-13.07	-13.02	2.02	-4.38
Body weight (kg)				
Baseline (mean)	88.94	87.10	65.60	65.93
LS mean change from baseline‡	-0.36	-1.55	-0.03	-0.48

ITT population = all randomized patients.

* 16% of patients in ADLYXIN and 13% in the placebo had missing HbA1c data at Week 24 with basal insulin +/- metformin in the ITT population.

† Conducted in an Asian population. 8% of patients in ADLYXIN and 6% of patients in placebo had missing HbA1c data at Week 24 with basal insulin +/- sulfonylurea in the ITT population.

‡ Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.

§ Patients with missing HbA1c value at Week 24 were considered nonresponders.

In a 24-week study, 446 patients with type 2 diabetes, inadequately controlled on diet exercise and on insulin glargine and metformin with or without thiazolidinediones, were randomized to ADLYXIN 20 mcg once daily or placebo. The mean age of the study population was 56.2 years, and mean duration of type 2 diabetes mellitus was 9.1 years; 49.8% were male, 74.4% were White, 4.5% were Black or African American, 22.6% were Hispanic, and 3.8% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 32 kg/m^2. At baseline, the mean insulin glargine dose was 44.5 units, the mean metformin dose was 2049 mg and 12.1% of individuals were receiving thiazolidinedione.

Compared with placebo, treatment with ADLYXIN 20 mcg once daily resulted in statistically significant reductions in HbA1c from baseline at Week 24 (see Table 10).

Table 10: Placebo-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with Insulin Glargine (24-week results) – ITT Population

Background Therapy	with Insulin Glargine and Metformin +/- Thiazolidinediones*	
	Placebo (N=223)	ADLYXIN 20 mcg (N=223)
HbA_{1c} (%)		
Baseline (mean)	7.60	7.56
LS mean change from baseline†	-0.42	-0.70

Difference from placebo (95% CI)		-0.28 (-0.434, -0.123) (p=0.0005)
Patients (%) achieving HbA_{1c} <7.0%‡	39	50
Fasting Plasma Glucose (FPG) (mg/dL)		
Baseline (mean)	120.67	117.99
LS mean change from baseline†	6.05	5.74
Body weight (kg)		
Baseline (mean)	86.75	87.31
LS mean change from baseline†	1.09	0.31
Difference from placebo (95% CI)		-0.78 (-1.388, -0.168) (p=0.0125)

ITT population = all randomized patients.
* 9% of patients in ADLYXIN and 5% in the placebo had missing HbA1c data at Week 24 in the ITT population.
† Using multiple imputation with respect to jump to placebo for missing data at Week 24 in the ADLYXIN group.
‡ Patients with missing HbA1c value at Week 24 were considered nonresponders.

In a 26-week open-label study, 894 patients with type 2 diabetes inadequately controlled on diet, exercise and basal insulin combined with 1 to 3 oral antidiabetic agents were randomized to ADLYXIN 20 mcg once daily or insulin glulisine once daily (QD) or insulin glulisine three times a day (TID) combined with insulin glargine with or without metformin. The mean age of the study population was 59.8 years, and mean duration of type 2 diabetes mellitus was 12.2 years; 45.3% were male, 92.6% were White, 4.0% were Black or African American, 21.1% were Hispanic, and 5.6% had an eGFR <60 mL/min/1.73 m^2. The mean BMI was 32 kg/m^2. At baseline, the mean insulin glargine dose was 65.9 units and 87.4% of individuals were receiving metformin.

ADLYXIN 20 mcg once daily met the prespecified noninferiority margin of 0.4% versus insulin glulisine QD and TID for the difference in HbA1c reduction from baseline. However in this study, ADLYXIN provided less HbA1c reduction than insulin glulisine TID and the difference was statistically significant (p=0.0002).

Table 11: Active-Controlled Study in Patients with Type 2 Diabetes Mellitus in Combination with a Basal Insulin with or without Metformin (26-week treatment period results) – ITT population

	ADLYXIN (N=298)	**Insulin Glulisine QD (N=298)**	**Insulin Glulisine TID (N=298)**
HbA1c (%)			
Baseline	7.77	7.73	7.79
LS Mean change from baseline*	-0.57	-0.53	-0.80
LS mean difference vs insulin glulisine*		-0.04	0.23
95% CI		(-0.161 to 0.080)	(0.112 to 0.352) (p=0.0002)
Patients (%) achieving HbA1c <7.0%†	38.6	36.6	47.7
Fasting Plasma Glucose (FPG) (mg/dL)			
Baseline	118.55	123.21	119.80
LS Mean change from baseline*	-3.39	-3.68	-1.42
Body weight (kg)			
Baseline	90.06	88.45	90.08
LS Mean change from baseline*	-0.64	0.98	1.26
LS mean difference vs insulin glulisine*			-1.91

	ADLYXIN (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)
95% CI			(-3.103 to -0.713) (p=0.0018)

ITT population = all randomized patients. Noninferiority margin = 0.4%.
12% of patients in ADLYXIN, 8% in glulisine QD and 5.0% in glulisine TID had missing HbA1c data at Week 26 in the ITT population.
***** Using multiple imputation with respect to use the baseline value for missing data at Week 26 in each group.
† Patients with missing HbA1c value at Week 26 were considered nonresponders.

14.6 ELIXA Cardiovascular Outcome Study

The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with ADLYXIN in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome event. The primary composite endpoint was the time to the first occurrence of a major adverse cardiovascular event or MACE+, defined as any of the following positively adjudicated events: Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, or hospitalization for unstable angina. The study was designed as a noninferiority trial with a prespecified risk margin of 1.3 for the hazard ratio comparing ADLYXIN to placebo.

Overall, 6068 patients were randomized 1:1 to either placebo or ADLYXIN 20 mcg (following a starting dose of 10 mcg during the first 2 weeks) and were included in the primary analyses. The demographics and baseline characteristics were well-balanced between treatments. The median age at study entry was 60 years. Approximately 69% of the patients were males and 75% were Caucasian. The majority of patients were either obese or overweight with a median BMI of 29.4 kg/m^2. The mean duration of diabetes was 9.3 years. More than 75% of patients had impaired renal function and more than 20% had an estimated GFR less than 60 mL/min/ 1.73 m^2. Use of CV medications at baseline was similar between treatments; platelet aggregation inhibitors (aspirin and/or clopidogrel) were used by 97.5% of patients, statins by 92.7%, ACE inhibitors and/or angiotensin II antagonists by 86.8%, and beta-blockers by 84.4%. Prior to study entry, 93.9% of patients used at least 1 glucose-lowering medication, including metformin (69.9%), sulfonylureas (37.3%) and insulin (47.6%). During the study, antidiabetic medications were adjusted by the investigators per the local standard of care.

Ninety-six percent of the patients in both treatment groups completed the study in accordance with the protocol, and the vital status was known at the end of the study for 99.0% and 98.6% of the patients in the ADLYXIN and placebo group, respectively. Median treatment duration was 22.4 months in the ADLYXIN group and 23.3 months in the placebo group, and the median duration of study follow-up was 25.8 and 25.7 months, respectively.

The results of the primary composite cardiovascular endpoint are shown in Table 12. The hazard ratio (HR) for ADLYXIN versus placebo was 1.02, with an associated 2-sided 95% confidence interval (CI) of 0.89 to 1.17. The upper bound of this confidence interval, 1.17, excluded a risk margin larger than 1.3.

Table 12: Analysis of the Primary Cardiovascular Endpoint (time to the first occurrence of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) – ITT Population

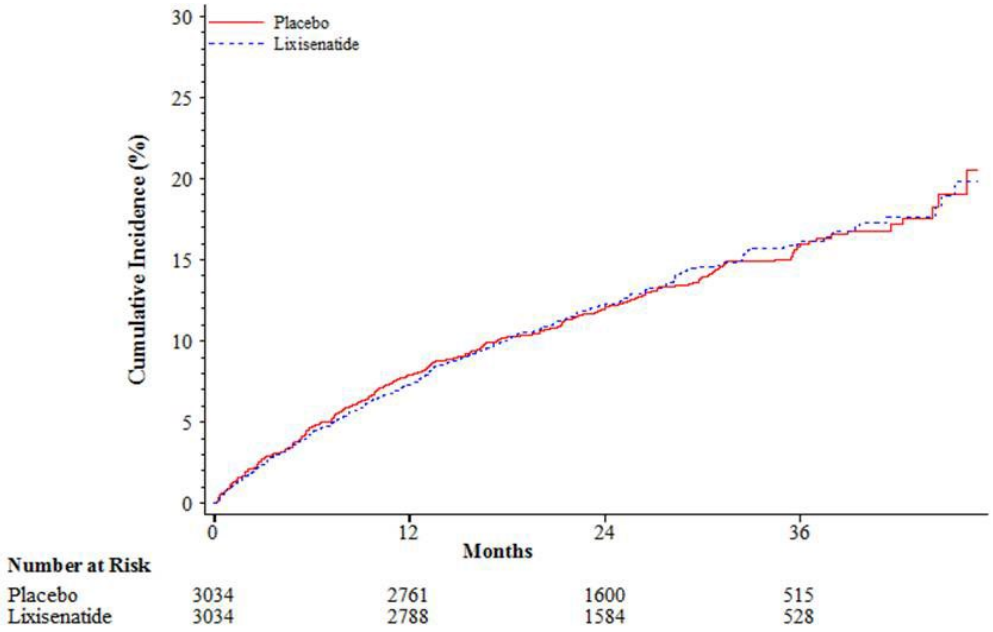
	Placebo	ADLYXIN	Hazard ratio

	(N=3,034)	(N=3,034)	(95% CI)
Primary composite CV event			1.02 (0.89, 1.17)
No. of patients with event (%)	399 (13.2%)	406 (13.4%)	
Total Person Year	6328.2	6356.8	
Incidence Rate	6.31	6.39	
Component CV event			
Cardiovascular death	93 (3.1%)	88 (2.9%)	
Nonfatal myocardial infarction	247 (8.1%)	255 (8.4%)	
Nonfatal stroke	49 (1.6%)	54 (1.8%)	
Hospitalization for unstable angina	10 (0.3%)	9 (0.3%)	

CI: confidence interval, CV: cardiovascular.
Only positively adjudicated events by the Cardiovascular Events Adjudication Committee are included.

The Kaplan-Meier based cumulative event probability is presented in Figure 1 for the time to first occurrence of the primary CV composite endpoint by treatment arm.

Figure 1: Kaplan-Meier Cumulative Curves of the Primary CV Endpoint (time to the first occurrence of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) – ITT Population



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADLYXIN (lixisenatide) injection is a clear and colorless solution supplied in a 3 mL single-patient-use pen.

The green starter pen is 50 mcg/mL and delivers 14 doses of 10 mcg. The burgundy maintenance pen is 100 mcg/mL and delivers 14 doses of 20 mcg.

The following packages are available:

- Starter Pack, NDC 0024-5745-02: For treatment initiation, Starter Pack contains 1 single-

patient-use prefilled green pen of ADLYXIN 10 mcg (NDC 0024-5741-01) and 1 single-patient-use prefilled burgundy pen of ADLYXIN 20 mcg (NDC 0024-5740-00).

- Maintenance Pack, NDC 0024-5747-02: Contains 2 single-patient-use prefilled burgundy pens for ADLYXIN 20 mcg (NDC 0024-5740-00).

16.2 Storage and Handling

Prior to first use, ADLYXIN should be stored in a refrigerator, 36°F to 46°F (2°C to 8°C). Do not freeze. Keep the prefilled pen in the original package to protect it from light.

After first use, store up to 86°F (30°C). Replace the pen cap after each use to protect from light. Discard pen 14 days after first use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Anaphylaxis and Serious Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, including anaphylaxis, have been reported in clinical trials of ADLYXIN and during postmarketing use of GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, inform patients that they must stop taking ADLYXIN and seek medical advice promptly *[see Warnings and Precautions (5.1)]*.

Acute Pancreatitis

Inform patients of the potential risk for acute pancreatitis and its symptoms: severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting. Instruct patients to discontinue ADLYXIN promptly and contact their physician if pancreatitis is suspected *[see Warnings and Precautions (5.2)]*.

Never Share ADLYXIN Pen Between Patients

Advise patients that they should never share ADLYXIN pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.3)]*.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia increased when ADLYXIN is used in combination with a sulfonylurea or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.4)]*.

Acute Kidney Injury Due to Volume Depletion

Inform patients of the potential risk of acute kidney injury due to dehydration associated with gastrointestinal adverse reactions. Advise patients to take precautions to avoid fluid depletion. Inform patients of the signs and symptoms of acute kidney injury and instruct them to promptly report any of these signs or symptoms or persistent (or extended) nausea, vomiting, and diarrhea to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.6)]*.

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.8)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that ADLYXIN may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ADLYXIN *[see Warnings and Precautions (5.9)]*.

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)]*.

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MEDICATION GUIDE
ADLYXIN® (ad-LIX-in)
(lixisenatide)
injection, for subcutaneous use

What is the most important information I should know about ADLYXIN? ADLYXIN may cause serious side effects including inflammation of the pancreas (pancreatitis),

Stop using ADLYXIN and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.

What is ADLYXIN?

ADLYXIN is an injectable prescription medicine that is used along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes.

It is not known if ADLYXIN is safe and effective in children.

Who should not use ADLYXIN?

Do not use ADLYXIN if you:

- have had a serious allergic reaction to lixisenatide or any of the ingredients in ADLYXIN. See the end of this Medication Guide for a complete list of ingredients in ADLYXIN. See "**What are the possible side effects of ADLYXIN?**" for symptoms of a serious allergic reaction.

Before using ADLYXIN, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had problems with your pancreas.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are scheduled to have surgery or other procedures that use general anesthesia or deep sleepiness (deep sedation).
- are pregnant or plan to become pregnant. It is not known if ADLYXIN will harm your unborn baby. Tell your healthcare provider if you are pregnant or plan to become pregnant while using ADLYXIN.
- are breastfeeding or plan to breastfeed. It is not known if ADLYXIN passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you use ADLYXIN.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. ADLYXIN may affect the way some medicines work and some medicines may affect the way ADLYXIN works.

Before using ADLYXIN, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

Especially tell your healthcare provider if you take:

- antibiotics or the pain reliever, acetaminophen. Take these medicines at least 1 hour before using ADLYXIN. If you must take these medicines, take them with a meal or a snack. You should not take these medicines at the same time that you take ADLYXIN.
- birth control pills that are taken by mouth (oral contraceptives). ADLYXIN may lower the amount of the medicine in your blood from your birth control pills and they may not work as well to prevent pregnancy. Take your birth control pill at least 1 hour before your injection of ADLYXIN or at least 11 hours after your ADLYXIN injection.

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 ADLYXIN?

- Read the **Instructions for Use** that comes with ADLYXIN.
- Use ADLYXIN 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 ADLYXIN before you use it for the first time.**
- Inject your dose of ADLYXIN under the skin (subcutaneously) of your abdomen, thigh or upper arm. **Do not** inject into a muscle (intramuscularly) or vein (intravenously).
- Use **ADLYXIN 1 time each day within 60 minutes (1 hour) before the first meal of the day and at the same time each day**.
- If you miss a dose of ADLYXIN, take it within 1 hour before your next meal.
- Check the label on the pen each time you give your ADLYXIN injection to make sure you are using the correct medicine.
- **You must activate each ADLYXIN pen before you use it for the first time.**
- Change (rotate) your injection sites within the area you chose with each dose. **Do not** use the same spot for each injection.
- **Do not re-use or share your needles with other people.** You may give other people a serious infection or get a serious infection from them
- If you take too much ADLYXIN, call your healthcare provider or the Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of ADLYXIN?

ADLYXIN may cause serious side effects including:

- See **"What is the most important information I should know about ADLYXIN?"**
- **severe allergic reactions.** Stop taking ADLYXIN and get medical help right away if you have any symptoms of a severe allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you use ADLYXIN with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. The dose of your sulfonylurea or insulin medicine may need to be lowered while you use ADLYXIN.
- **Signs and symptoms of low blood sugar may include:**
  - Dizziness or light-headedness
  - sweating
  - confusion or drowsiness
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - hunger
  - weakness
  - feeling jittery
- **dehydration leading to kidney problems.** Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems. It is important for you to drink fluids to help reduce your chance of dehydration. Tell your healthcare provider right away if you have nausea, vomiting, or diarrhea that does not go away.
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use ADLYXIN. Tell your healthcare provider if you have stomach problems that are severe or will not go away.

- **gallbladder problems.** Gallbladder problems have happened in some people who take ADLYXIN. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools
- **food or liquid getting into the lungs during surgery or other procedures that use general anesthesia or deep sleepiness (deep sedation).** ADLYXIN may increase the chance of food getting into your lungs during surgery or other procedures. Tell all your healthcare providers that you are taking ADLYXIN before you are scheduled to have surgery or other procedures.

The most common side effects of ADLYXIN include:

- nausea
- vomiting
- headache
- diarrhea
- feeling dizzy

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of ADLYXIN. 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 ADLYXIN?

- Store your new, unused ADLYXIN pen in the refrigerator at 36°F to 46°F (2°C to 8°C).
- After activation, store your ADLYXIN pen at room temperature no higher than 86°F (30°C).
- Do not freeze ADLYXIN pens and do not use ADLYXIN if it has been frozen.
- Protect the pen from light.
- Replace the pen cap after each use to protect the container window from light.
- After activation, use the ADLYXIN pen for up to 14 days. Throw away the used ADLYXIN pen after 14 days, even if there is some medicine left in the pen.
- Do not use ADLYXIN past the expiration date printed on the label of the carton and pen.
- Do not store the ADLYXIN 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 ADLYXIN pen.

Keep your ADLYXIN pen, pen needles, and all medicines out of the reach of children.

General information about the safe and effective use of ADLYXIN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADLYXIN for a condition for which it was not prescribed. Do not give ADLYXIN 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 ADLYXIN that is written for health professionals.

What are the ingredients in ADLYXIN?

Active ingredient: lixisenatide
Inactive ingredients: glycerol 85%, metacresol, methionine, sodium acetate trihydrate, and Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide solution are added as needed to adjust the pH.

Manufactured by: sanofi-aventis U.S. LLC, Morristown, NJ 07960, A SANOFI COMPANY
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For more information, go to www.ADLYXIN.com or call sanofi-aventis at 1-800-633-1610.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: May 2025

INSTRUCTIONS FOR USE
ADLYXIN® (ad-LIX-in)
(lixisenatide)
Injection, for subcutaneous use

One pre-filled pen contains 14 doses, each dose contains **20 micrograms (mcg) in 0.2 mL.**

Section 1 – Important Information

Read these instructions carefully before using your ADLYXIN pen.

Keep this leaflet for future reference.

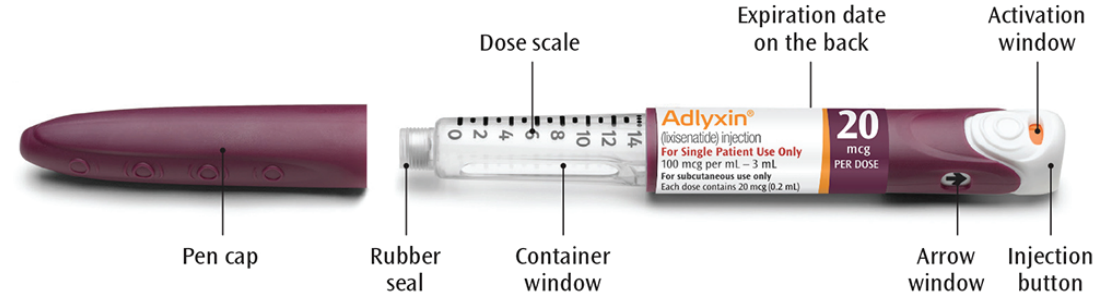
Do not share your ADLYXIN pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

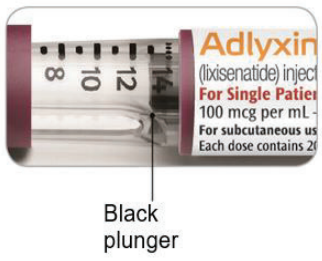
ADLYXIN pen Information

- ADLYXIN comes as a single-patient-use prefilled pen for injection.
- **Inject 1 dose per day.**
- There is no need to measure each dose.
- **Talk with your healthcare provider about how to use the ADLYXIN pen and to inject correctly before using it.**
- If you cannot follow all the instructions completely on your own or are not able to handle the pen (for example, if you have vision problems), only use it if you have help.

About Your ADLYXIN Pen

Burgundy 20 mcg ADLYXIN pen



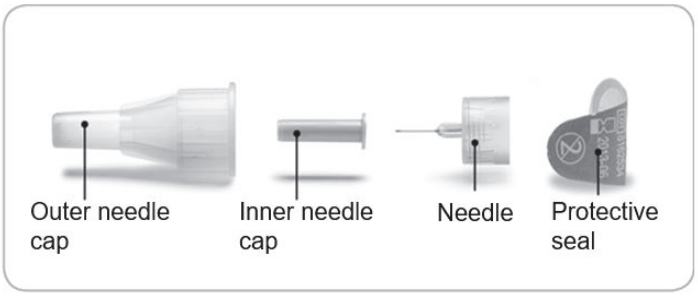


The plunger will move along the dose scale after each injection. In the example above, the dose number shows there are 13 injections left in the ADLYXIN pen.

Reference ID: 5598371
Reference ID: 5471638

- Always check the label to make sure you have the correct ADLYXIN pen. Also, check that it has not passed the expiration date printed on the ADLYXIN pen. Do not use ADLYXIN past the expiration date. Using the wrong medicine could be harmful to your health.
- Inject ADLYXIN only by using this pen injector. Never use a syringe to withdraw ADLYXIN from the pen.

About your pen needles (supplied separately)



- **Pen needles are not included with your pen.**
- Always use a new needle for each injection. This helps prevent contamination of ADLYXIN or possible needle blockage.
- Only use needles that have been approved for use with ADLYXIN. The ADLYXIN pen may be used with certain pen needles from Becton Dickinson, Ypsomed, and Owen Mumford that are 8 mm long or shorter. Ask your healthcare provider which needle gauge and length is best for you.
- Do not reuse or share needles with another person.

Section 2 – Getting Started

- **Activate the pen on the same day as your first injection with your new pen.**

First activate your new pen

- **Before injecting the first dose of ADLYXIN**, you must activate the new pen. This is a one-time process called “activation.” **Step 1 to Step 5** below show you how to do this.
- Activation is done to make sure that the pen is working correctly and that the dose for your first injection is correct.
- **Do not repeat** the activation process or you will not receive 14 doses from your ADLYXIN pen.

The pictures below show how the injection button of your pen changes after activation.

Before activation
(orange window)

The pen is not activated when the activation window is orange. The pen must be activated before injecting your first dose of ADLYXIN.

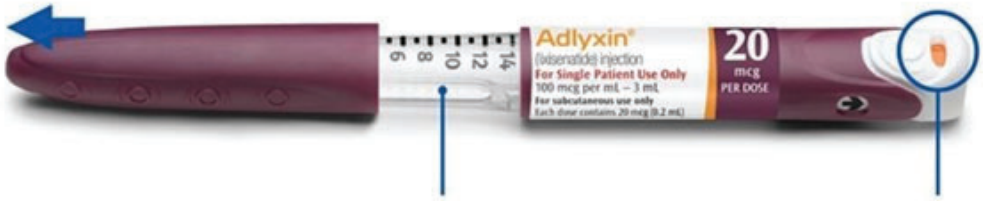
After activation
(white window)

The pen is activated and ready for injections when the activation window is white.

ReferenceID: 5598371
ReferenceID: 5471638

How to activate your new ADLYXIN pen

Step 1. Pull off the pen cap and check the pen

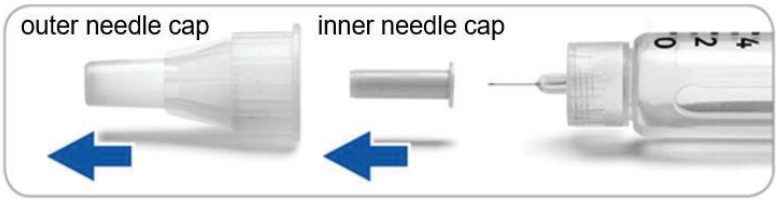


Check the liquid by looking through the container window. It should be clear and colorless with no particles. If not, do not use this pen. Contact your healthcare provide. Small air bubbles in the liquid are normal. See the **Question and Answers** section at the end of this Instruction for Use.

Check that the activation window is orange.

Step 2. Screw needle on and remove needle caps

- Always use a **new needle** for activation.
- Remove the protective seal from the outer needle cap.
- Line up the needle with the pen. Push the outer needle cap containing the needle straight onto the pen, then screw the needle on until secure.



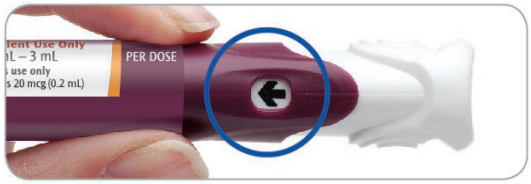
- **Pull off** (do not unscrew) the outer needle cap.
  - Pull off the inner needle cap and throw it away.
  - Keep the outer needle cap to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

Step 3. Pull the injection button out

Reference ID: 5598371
Reference ID: 5471638

The arrow in the window will be pointing towards the injection button.

Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4. Firmly press and hold the injection button to remove the liquid

- **Do not** inject into the body.
- Point the needle into a container (like a paper cup or tissue).
- **Firmly press the injection button all the way in** to discard the liquid. You may feel or hear a “click.”
- Keep the injection button pressed in **and slowly count to 2**, which is equal to 2 seconds.
- If no liquid comes out of your pen, see the **Questions and Answers** section at the end of this Instructions for Use.
- Check that the activation window is now white.

Step 5. The pen is now ready for use.

- **Do not activate this pen again.**

For your first injection, go directly to Section 3 – Step 3.

- You **do not** need to replace the needle between activation and first injection if you inject yourself immediately after activation.

Section 3 – Daily use of pen

Inject only 1 dose each day.

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Reference ID: 5471638

Check to make sure the activation window is white before continuing in this section.

Step 1. Pull off pen cap and check pen

Check the label on your pen to make sure that you have the correct medicine.

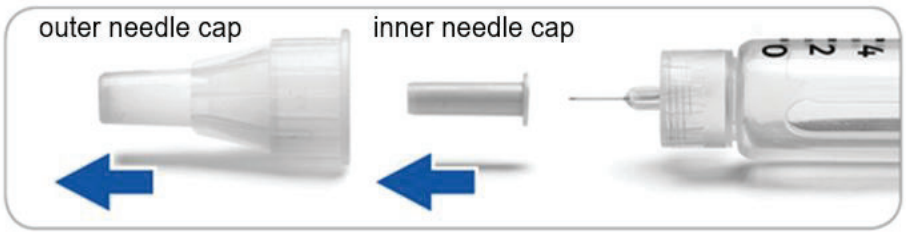
Check the liquid. It should be clear and colorless with no particles. If not, do not use the pen. Call your healthcare provider. Tiny air bubbles in the liquid are normal. See the **Questions and Answers** section at the end of this Instructions for Use.

Check the number of doses remaining in the pen. This is shown by placement of the black plunger.

Check that the activation window is White. If it is Orange, go to Section 2.

Step 2. Attach a new needle and remove the needle caps

- Always use a **new needle** for each injection.
- Remove the protective seal from the outer needle cap.
- Line up the needle with the pen. Put the outer needle cap containing the needle straight on the pen, then screw the needle on until secure.

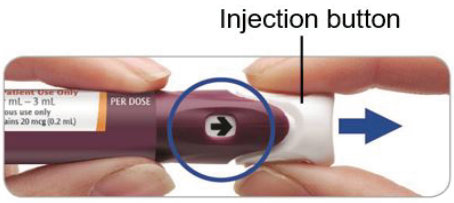


- **Pull off** (do not unscrew) the outer needle cap.
  - Pull off the inner needle cap and throw it away.
  - Keep the outer needle cap to remove the needle later.

Reference ID: 5471638

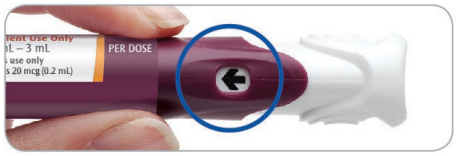
- Take care not to injure yourself when the needle is exposed.

Step 3. Pull the injection button out



The arrow in the window will be pointing towards the injection button.

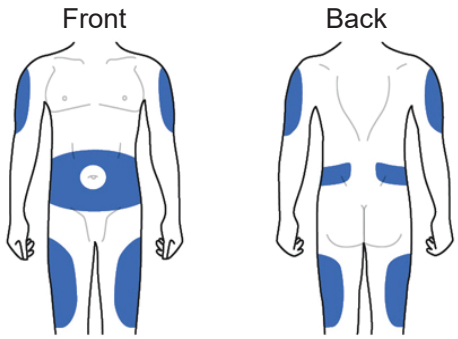
Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4. Choosing Injection Sites

Injection sites



ADLYXIN must be injected under the skin and can be injected in any of the areas shown above in blue. These areas include the thigh, abdomen, or upper arm. Ask your healthcare provider about how to inject correctly.

Step 5. Press and hold the injection button to inject the dose

Reference ID: 5598371
Reference ID: 5471638

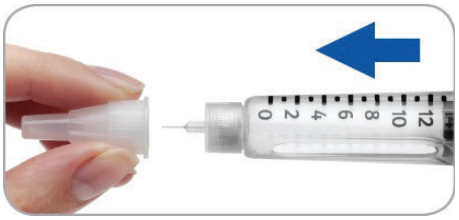
- Grasp a fold of skin and insert the needle (see the Injection sites section about where to inject).
- **Press the injection button all the way in. You may feel or hear a "click."**
- **Keep the injection button pressed in, hold the pen in place and slowly count to 2**, which is equal to 2 seconds, **before you pull the needle out of the skin.**

If you do not hold the injection button in or if you remove the injector too early you may not get the full dose.

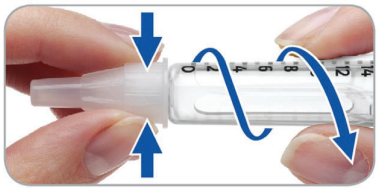
Your dose has now been given. Pull the needle out of your skin.

Step 6. Remove and throw away needle after each injection

- **Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap.**
- **Then push firmly on.**
- The needle can puncture the cap if it is recapped at an angle.



- **Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.**
- Try again if the needle does not come off the first time.



- Replace the pen cap.

- Put the needle in a puncture-resistant container (or as instructed by your healthcare provider).

Step 7. Repeat all steps in Section 3 for each injection.

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Throw away a pen 14 days after activation, even if there is some medicine left.

Table of activation and disposal

In the table, write the date when you activated your pen and the date to throw it away 14 days later.

Pen	Date of activation	Date to throw away
1		
2		
3		
4		
5		
6		

Storage

General information

- Keep your ADLYXIN pen in a safe place out of the reach and sight of children.
- Protect your ADLYXIN pen from dust and dirt.
- Replace the pen cap after each use in order to protect the container window from light.
- Protect the ADLYXIN pen from light.
- Do not use ADLYXIN after the expiration date, which is stated on the label and on the carton. The expiration date refers to the last day of that month.

Before activation of the pen:

- Store your unused ADLYXIN pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze ADLYXIN pens and do not use ADLYXIN if it has been frozen.
- Allow your pen to warm at room temperature before using.

After activation of the pen:

- After activation, store your ADLYXIN pen at room temperature no higher than 86°F (30°C).
- Do not store your ADLYXIN pen with the needle attached. An attached needle might lead to contamination and may cause air bubbles which might affect your dose of medicine.
- After your ADLYXIN pen is activated it can be used for up to 14 days. Throw away a used ADLYXIN pen after 14 days. Do this even if there is some medicine left in the pen.

Throwing your pen away

- Replace the pen cap before throwing away (disposing of) your ADLYXIN pen.
- Put the used ADLYXIN pen in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) the ADLYXIN pen and loose needles in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
  - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container.

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There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Maintenance

- Handle your ADLYXIN pen with care.
- You can clean the outside of your ADLYXIN pen by wiping it with a damp cloth.
- Do not soak, wash, or put liquid on (lubricate) your ADLYXIN pen. This may damage it.
- If you think your ADLYXIN pen may be damaged, do not use it. Get a new one. Do not try to repair the pen.

Questions and Answers

What do I do if I forget to activate the ADLYXIN pen or inject myself before activation?
If you have injected yourself before activating the pen, do not correct this by giving yourself a second injection. Contact your healthcare provider for advice on checking your blood sugar.

What do I do if there are air bubbles in the container?
Small air bubbles in the container are normal and they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your healthcare provider if you need help.

What do I do if no liquid comes out during activation?
The needle may be blocked or not properly attached. Remove the needle from the pen, attach a new needle, and repeat **Step 4 and Step 5** of Section 2 only. If still no liquid comes out, your ADLYXIN pen may be damaged. Do not use this ADLYXIN pen. Contact your healthcare provider for help.

What do I do if it is hard to press the injection button all the way in?
The needle may be blocked or not properly attached. Pull the needle out of your skin and remove the needle from the pen. Attach a new needle and repeat **Step 5 and Step 6** of Section 3 only. If it is still hard to press in the injection button, your ADLYXIN pen may be damaged. Do not use this ADLYXIN pen. Contact your healthcare provider for help.

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Bridgewater, NJ 08807
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If you have any questions about ADLYXIN or about diabetes, ask your healthcare provider or call sanofi-aventis U.S. LLC at 1-800-633-1610.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: July 2021

Reference ID: 5598371
Reference ID: 5471638

INSTRUCTIONS FOR USE
ADLYXIN® (ad-LIX-in)
(lixisenatide)
Injection, for subcutaneous use

Starter pack - Contains 2 prefilled pens each with **14** doses.

One **10 microgram (mcg)** pen, each dose contains **10 mcg in 0.2 mL.**
One **20 microgram (mcg)** pen, each dose contains **20 mcg in 0.2 mL.**

Section 1 – Important Information

Read these instructions carefully before using your ADLYXIN pens.

Keep this leaflet for future reference.

Do not share your ADLYXIN 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.

ADLYXIN pen Information

- ADLYXIN comes as a single-patient-use prefilled pen for injection.
- **Inject 1 dose per day.**
- There is no need to measure each dose.
- **Talk with your healthcare provider about how to use the ADLYXIN pen and to inject correctly before using it.**
- If you cannot follow all the instructions completely on your own or are not able to handle the pen (for example, if you have vision problems), only use it if you have help.

About Your ADLYXIN Starter Pack

The ADLYXIN Starter pack includes 2 different colored pens that contain different strengths of ADLYXIN. Both pens are used in the same way.

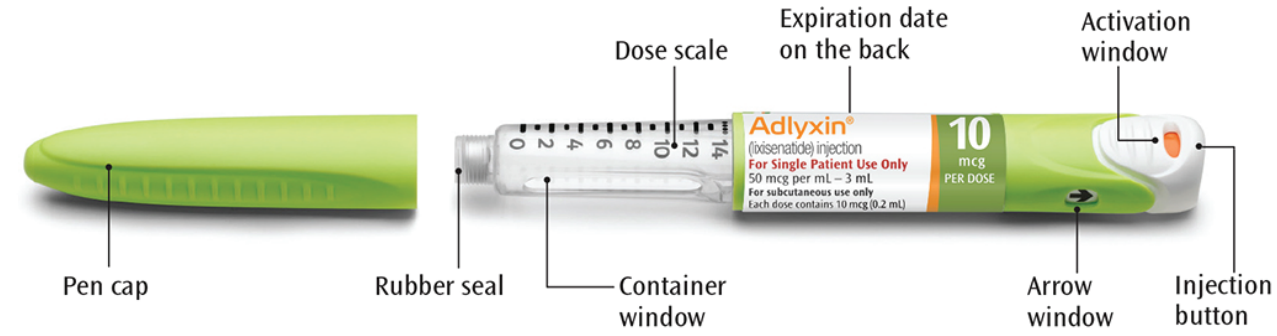
- The green pen contains 14 pre-set doses. Each dose contains 10 mcg of ADLYXIN.
- The burgundy pen contains 14 pre-set doses. Each dose contains 20 mcg of ADLYXIN.

You must start your treatment with the green 10 mcg ADLYXIN pen. You must first use all 14 doses from this pen. Then use the burgundy 20 mcg ADLYXIN pen.

About Your ADLYXIN Pens

Green 10 mcg ADLYXIN pen

Reference ID: 5598631

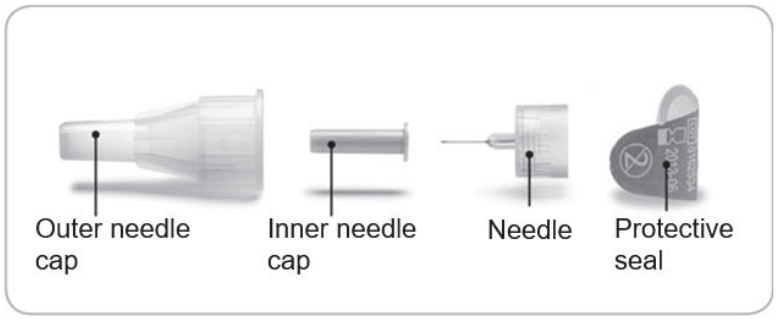


The plunger will move along the dose scale after each injection. In the example above, the dose number shows there are 13 injections left in the ADLYXIN pen.

Burgundy 20 mcg ADLYXIN pen

- Always check the label to make sure you have the correct ADLYXIN pen. Also, check that it has not passed the expiration date printed on the ADLYXIN pen. Do not use ADLYXIN past the expiration date. Using the wrong medicine could be harmful to your health.
- Inject ADLYXIN only by using this pen injector. Never use a syringe to withdraw ADLYXIN from the pen.

About your pen needles (supplied separately)



- **Pen needles are not included with your pen.**
- Always use a new needle for each injection. This helps prevent contamination of ADLYXIN or possible needle blockage.

Reference ID: 5598631

- Only use needles that have been approved for use with ADLYXIN. The ADLYXIN pen may be used with certain pen needles from Becton Dickinson, Ypsomed, and Owen Mumford that are 8 mm long or shorter. Ask your healthcare provider which needle gauge and length is best for you.
- Do not reuse or share needles with another person.

Section 2 – Getting Started

- **Begin with the green 10 mcg ADLYXIN pen.**
- **Do not activate the burgundy 20 mcg ADLYXIN pen until you have finished the green pen**.

First activate your new pen

- **Before injecting the first dose of ADLYXIN**, you must activate the new pen. This is a one-time process called “activation.” **Step 1 to Step 5** below show you how to do this.
- Activation is done to make sure that the pen is working correctly and that the dose for your first injection is correct.
- **Do not repeat** the activation process or you will not receive 14 doses from your ADLYXIN pen.

The pictures below show how the injection button of your pen changes after activation.

Before activation (orange window)

The pen is not activated when the activation window is orange. The pen must be activated before injecting your first dose of ADLYXIN.

After activation (white window)

The pen is activated and ready for injections when the activation window is white.

How to activate your new ADLYXIN pen

Step 1. Pull off the pen cap and check the pen

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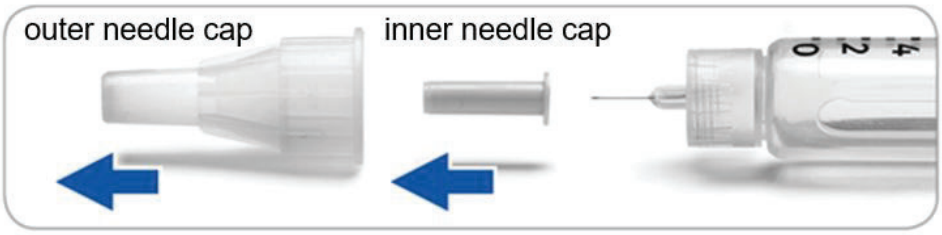
Check the liquid by looking through the container window. It should be clear and colorless with no particles. If not, do not use this pen. Contact your healthcare provide. Small air bubbles in the liquid are normal. See the **Question and Answers** section at the end of this Instruction for Use.

Check that the activation window is orange.

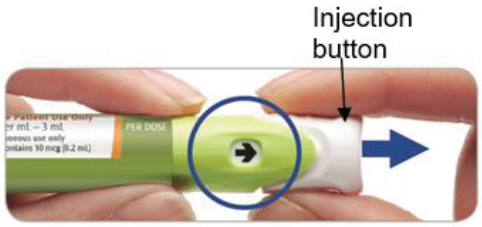
Step 2. Screw needle on and remove needle caps

- Always use a **new needle** for activation.
- Remove the protective seal from the outer needle cap.
- Line up the needle with the pen. Push the outer needle cap containing the needle straight onto the pen, then screw the needle on until secure.



- **Pull off** (do not unscrew) the outer needle cap.
  - Pull off the inner needle cap and throw it away.
  - Keep the outer needle cap to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

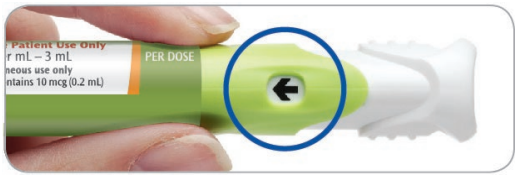
Step 3. Pull the injection button out



The arrow in the window will be pointing towards the injection button.

Reference ID: 5598631

Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4. Firmly press and hold the injection button to remove the liquid

- **Do not** inject into the body.
- Point the needle into a container (like a paper cup or tissue).
- **Firmly press the injection button all the way in** to discard the liquid. You may feel or hear a “click.”
- Keep the injection button pressed in and **slowly count to 2**, which is equal to 2 seconds.
- If no liquid comes out of your pen, see the **Questions and Answers** section at the end of this Instructions for Use.
- Check that the activation window is now white.

Step 5. The pen is now ready for use.

- **Do not activate this pen again.**

For your first injection, go directly to Section 3 – Step 3.

- You **do not** need to replace the needle between activation and first injection if you inject yourself immediately after activation.

Section 3 – Daily use of pen

Inject only 1 dose each day.

Check to make sure the activation window is white before continuing in this section.

Step 1. Pull off pen cap and check pen

Check the label on your pen to make sure you have the correct medicine.

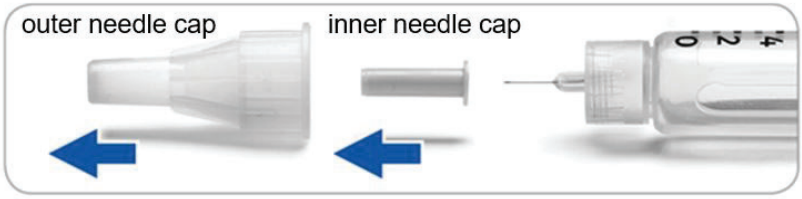
Check the liquid. It should be clear and colorless with no particles. If not, do not use the pen. Call your healthcare provider. Tiny air bubbles in the liquid are normal. See the **Questions and Answers** section at the end of this Instructions for Use.

Check the number of doses remaining in the pen. This is shown by the placement of the black plunger.

Check that the activation window is White. If it is Orange, go to Section 2.

Step 2. Attach a new needle and remove the needle caps

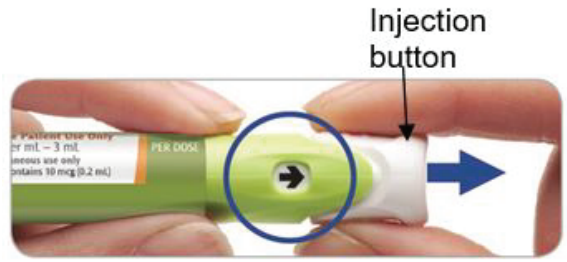
- Always use a **new needle** for each injection.
- Remove the protective seal from the outer needle cap.
- Line up the needle with the pen. Put the outer needle cap containing the needle straight on the pen, then screw the needle on until secure.



- **Pull off** (do not unscrew) the outer needle cap.
  - Pull off the inner needle cap and throw it away.
  - Keep the outer needle cap to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

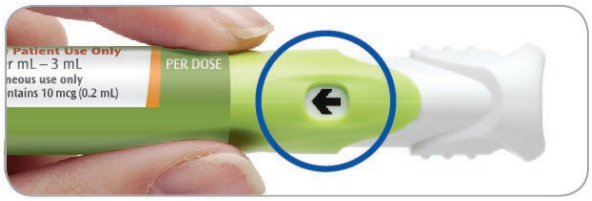
Step 3. Pull the injection button out

Reference ID: 5598631



The arrow in the window will be pointing towards the injection button.

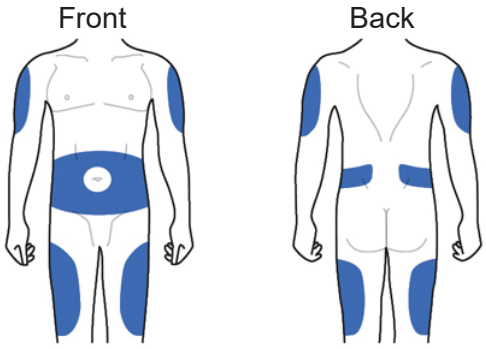
Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4. Choosing Injection Sites

Injection sites



ADLYXIN must be injected under the skin and can be injected in any of the areas shown above in blue. These areas include the thigh, abdomen, or upper arm. Ask your healthcare provider about how to inject correctly.

Step 5. Press and hold the injection button to inject the dose

Reference ID: 5[illegible]

- Grasp a fold of skin and insert the needle (see the Injection sites section about where to inject).
- **Press the injection button all the way in. You may feel or hear a "click."**
- **Keep the injection button pressed in, hold the pen in place and slowly count to 2,** which is equal to 2 seconds**, before you pull the needle out of the skin.**

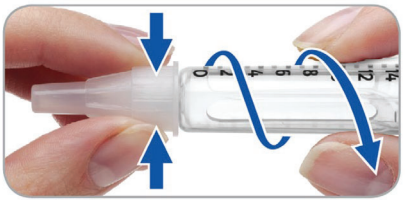
If you do not hold the injection button in or if you remove the injector too early you may not get the full dose.

Your dose has now been given. Pull the needle out of your skin.

Step 6. Remove and throw away needle after each injection

- **Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap.**
- **Then push firmly on.**
- The needle can puncture the cap if it is recapped at an angle.

- **Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.**
- Try again if the needle does not come off the first time.



- Replace the pen cap.

Reference ID: 5598631

- Put the needle in a puncture-resistant container (or as instructed by your healthcare provider).

Step 7. Repeat all steps in Section 3 for each injection.

Throw away a pen 14 days after activation, even if there is some medicine left.

After the green pen is thrown away continue to **Section 4** to begin using the burgundy pen.

Section 4 – Moving to the burgundy pen

Completed use of the green 10 mcg pen

The green 10 mcg ADLYXIN pen is empty when the black plunger has reached “0” on the dose scale and the injection button cannot be pulled out fully.

After the green 10 mcg ADLYXIN pen is empty you must continue your treatment the next day using the burgundy 20 mcg ADLYXIN pen. This is used in exactly the same way.

Use of burgundy 20 mcg pen

Burgundy 20 mcg pen activation

The burgundy 20 mcg ADLYXIN pen must also be activated before use. Follow all steps in Section 2.

Burgundy 20 mcg pen use

To inject a dose with the burgundy 20 mcg ADLYXIN pen, follow all steps in Section 3. Repeat Section 3 for your daily injections until your pen is empty.

Table of activation and disposal

In the table write the date when you activated your pen and the date to throw it away 14 days later.

Pen	Date of activation	Date to throw away
10 mcg	___ / ___ / ___	___ / ___ / ___

Reference ID: 5598631

20 mcg	___ / ___ / ___	___ / ___ / ___

Storage

General information

- Keep your ADLYXIN pens in a safe place out of the reach and sight of children.
- Protect your ADLYXIN pens from dust and dirt.
- Replace the pen cap after each use in order to protect the container window from light.
- Protect the ADLYXIN pen from light.
- Do not use ADLYXIN after the expiration date, which is stated on the label and on the carton. The expiration date refers to the last day of that month.

Before activation of the pen:

- Store your unused ADLYXIN pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze ADLYXIN pens and do not use ADLYXIN if it has been frozen.
- Allow your pen to warm at room temperature before using.

After activation of the pen:

- After activation, store your ADLYXIN pen at room temperature no higher than 86°F (30°C).
- Do not store your ADLYXIN pen with the needle attached. An attached needle might lead to contamination and may cause air bubbles which might affect your dose of medicine.
- After your ADLYXIN pen is activated it can be used for up to 14 days. Throw away a used ADLYXIN pen after 14 days. Do this even if there is some medicine left in the pen.

Throwing your pen away

- Replace the pen cap before throwing away (disposing of) your ADLYXIN pen.
- Put the used ADLYXIN pen in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) the ADLYXIN pen and loose needles in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
  - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Maintenance

- Handle your ADLYXIN pen with care.
- You can clean the outside of your ADLYXIN pen by wiping it with a damp cloth.

Reference ID: 5598631

- Do not soak, wash, or put liquid on (lubricate) your ADLYXIN pen. This may damage it.
- If you think your ADLYXIN pen may be damaged, do not use it. Get a new one. Do not try to repair the pen.

Questions and Answers

What do I do if I forget to activate the ADLYXIN pen or inject myself before activation?
If you have injected yourself before activating the pen, do not correct this by giving yourself a second injection. Contact your healthcare provider for advice on checking your blood sugar.

What do I do if there are air bubbles in the container?
Small air bubbles in the container are normal and they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your healthcare provider if you need help.

What do I do if no liquid comes out during activation?
The needle may be blocked or not properly attached. Remove the needle from the pen, attach a new needle, and repeat **Step 4 and Step 5** of Section 2 only. If still no liquid comes out, your ADLYXIN pen may be damaged. Do not use this ADLYXIN Starter pack. Contact your healthcare provider for help.

What do I do if it is hard to press the injection button all the way in?
The needle may be blocked or not properly attached. Pull the needle out of your skin and remove the needle from the pen. Attach a new needle and repeat **Step 5 and Step 6** of Section 3 only. If it is still hard to press in the injection button, your ADLYXIN pen may be damaged. Do not use this ADLYXIN starter pack. Contact your healthcare provider for help.

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Revised: July 2021

Reference ID: 5[illegible]