PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**ADLYXINE®**

lixisenatide injection

Solution for Injection in a pre-filled pen,

0.05 mg per mL (10 mcg/dose)
0.1 mg per mL (20 mcg/dose)

Glucagon-like peptide-1 (GLP-1) analogues

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	07/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ADLYXINE (lixisenatide injection) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with:

- metformin,
- a sulfonylurea (alone or with metformin),
- pioglitazone (alone or with metformin),
- a basal insulin (alone or with metformin),

when the therapy listed above does not provide adequate glycemic control (see14 CLINICAL TRIALS)

Limitations of Use

ADLYXINE has not been studied with short acting insulin.

ADLYXINE should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ADLYXINE have not been established in patients younger than 18 years of age, therefore ADLYXINE is not indicated in pediatric patients.

1.2 Geriatrics

Geriatrics (≥65 years of age): ADLYXINE should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out (see 7 WARNINGS AND PRECAUTIONS – Special Populations - Geriatrics).

2 CONTRAINDICATIONS

ADLYXINE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Hypersensitivity reactions, including anaphylaxis, have occurred with ADLYXINE (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- ADLYXINE is administered by subcutaneous injection once daily, within the hour prior to any meal of the day.
    - It is preferable that the prandial injection of ADLYXINE is performed before the same meal every day, when the most convenient meal has been chosen.

- ADLYXINE is to be injected subcutaneously in the thigh, abdomen or upper arm.
    - Injection sites within an injection area must be alternated from one injection to the next.
- ADLYXINE should not be administered intravenously or intramuscularly.

4.2 Recommended Dose and Dosage Adjustment

The starting dose is 10 mcg ADLYXINE once daily for 14 days. Increase the ADLYXINE dose to the maintenance dose of 20 mcg once daily starting on day 15.

If the 20 mcg daily maintenance dosage is not tolerated, the dosage can be temporarily reduced to 10 mcg once daily. Consider increasing the dosage to 20 mcg once daily within 4 weeks.

When ADLYXINE is added to a sulfonylurea or basal insulin, there is a potential risk of hypoglycemia. A reduction of the concomitantly administered sulfonylurea or basal insulin may be necessary based on clinical experience (see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS).

Special Populations

Geriatrics (≥65 years):

No dose adjustment is required based on age. In Phase 2 and 3 controlled clinical studies of ADLYXINE, including a specific study dedicated to non-frail diabetic older patients aged 70 years and over (see 14 CLINICAL TRIALS), a total of 2013 of the patients exposed to ADLYXINE were 65 years of age and over and 350 were 75 years of age and over. No overall differences were observed in safety or effectiveness between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (<18 years of age):

The safety and effectiveness of ADLYXINE have not been studied in the pediatric population. ADLYXINE should not be used in pediatric patients.

Hepatic Impairment:

No dosage adjustment is necessary for patients with hepatic impairment.

Renal Impairment:

No dosage adjustment is necessary for patients with mild (creatinine clearance: 60-90 mL/min) and moderate (creatinine clearance: 30-60 mL/min) renal impairment.

Therapeutic experience with ADLYXINE in patients with severe renal impairment is very limited, and there is no experience in patients with end stage renal disease or on dialysis. Therefore, use in these patients is not recommended.

4.4 Administration

Patients and caregivers should receive proper training prior to first use of ADLYXINE (see 11 STORAGE, STABILITY AND DISPOSAL and 12 SPECIAL HANDLING INSTRUCTIONS).

4.5 Missed Dose

If a dose of ADLYXINE is missed, it should be injected within the hour prior to the next meal. An extra dose should not be taken to make up for the missed dose.

5 OVERDOSAGE

During clinical trials, short term exposure of patients to lixisenatide at doses of up to 30 mcg twice a day resulted in an increased incidence of gastrointestinal adverse reactions.

In case of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and should include close monitoring of plasma glucose, hydration status and renal function. If ADLYXINE is to be continued, the ADLYXINE dose should be reduced to the prescribed dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Sterile solution for injection, in prefilled pen: 10 mcg /dose (0.05 mg/mL) 20 mcg /dose (0.1 mg/mL) Active ingredient: lixisenatide	Glycerol, hydrochloric acid/sodium hydroxide solution for pH adjustment, metacresol (2.7 mg/mL), methionine, sodium acetate trihydrate, water for injection

Packaging

ADLYXINE is supplied in a disposable pen containing a sterile solution for subcutaneous administration. Each prefilled pen contains 3 mL solution. The green starter pen delivers 14 doses of 10 mcg, and the burgundy maintenance pen delivers 14 doses of 20 mcg.

The following packages are available:

- Maintenance Pack: 2 prefilled burgundy pens for ADLYXINE 20 mcg.
- A pack size of 1 prefilled green pen for ADLYXINE 10 mcg.
- A pack size of 2 prefilled green pens for ADLYXINE 10 mcg.

Pen needles are not included in the packages.

7 WARNINGS AND PRECAUTIONS

General

ADLYXINE must not be administered by intravenous or intramuscular injection.

ADLYXINE pens should never be shared between patients, even if the needle is changed.

Carcinogenesis and Mutagenesis

Risk of thyroid C-cell tumours:

Lixisenatide administration to mice and rats for 2 years resulted in thyroid C-cell neoplasia. C cell carcinomas were confined to rats at human systemic lixisenatide exposure ratios ≥35-fold, while increased incidences of C-cell hyperplasia and adenoma occurred at exposure ratios of >128-fold in mice and ≥9-fold in rats, with a no-effect level not identified in rats (see16 NON-CLINICAL TOXICOLOGY).

Other GLP-1 receptor agonists have been shown to cause thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in rats and mice. The relevance of these results to humans has not yet been determined. Until further long-term data in humans are available, caution is advised when prescribing ADLYXINE in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Cardiovascular

Heart Rate Increase:

ADLYXINE causes an increase in heart rate in clinical trials in healthy subjects undergoing serial electrocardiogram (ECG) monitoring and in patients with type 2 diabetes mellitus undergoing 24 hour ambulatory heart rate monitoring (see 10 CLINICAL PHARMACOLOGY– Pharmacodynamics). Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as tachyarrhythmias (see 9 DRUG INTERACTIONS).

PR Interval Prolongation:

ADLYXINE causes a prolongation of the PR interval of the ECG (see 10 CLINICAL PHARMACOLOGY – Pharmacodynamics). Caution should be observed in patients with pre-existing conduction system abnormalities (e.g. marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g. tachyarrhythmias).

Physicians should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug (see 9 DRUG INTERACTIONS).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed.

When used in combination with a sulfonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

Endocrine and Metabolism

Hypoglycemia:

Use with a sulfonylurea or basal insulin: Patients receiving ADLYXINE in combination with a sulfonylurea or basal insulin have an increased risk of hypoglycemia (see 8 ADVERSE REACTIONS). Reduction of the dose of the sulfonylurea or basal insulin may be considered to reduce the risk of hypoglycemia (see 4 DOSAGE AND ADMINISTRATION).

Gastrointestinal

Patients with Severe Gastrointestinal Disease:

Use of glucagon-like peptide-1 (GLP-1) receptor agonists, including ADLYXINE, is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhea. ADLYXINE has not been studied in patients with severe gastrointestinal disease, including gastroparesis, a history of stomach/gastric surgery, or inflammatory bowel disease, and therefore, the use of ADLYXINE is not recommended in these patients.

ADLYXINE can slow gastric emptying, which can reduce the rate of absorption of orally administered drugs (see 9 DRUG INTERACTIONS).

Acute gallbladder disease:

The use of GLP-1 receptor agonists has been associated with acute gallbladder disease. Acute gallbladder events such as cholelithiasis or cholecystitis have been reported in patients treated with lixisenatide. Patients should be informed of the characteristic symptoms of acute gallbladder disease: upper abdominal pain, fever, nausea, vomiting, and jaundice. If cholelithiasis is suspected, gallbladder exams and follow up are indicated.

Hepatic/Biliary/ Pancreatic

Pancreatitis:

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported in patients treated with GLP-1 receptor agonists, and cases of pancreatitis have occurred in patients treated with ADLYXINE during clinical trials (see 8 ADVERSE REACTIONSS). Patients should be informed of the characteristic symptoms of acute pancreatitis, such as persistent, severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting. If pancreatitis is suspected, ADLYXINE should be discontinued and appropriate management initiated promptly. If pancreatitis is confirmed, ADLYXINE should not be restarted. Consider other antidiabetic therapies in patients with a history of pancreatitis or in patients with other risk factors for pancreatitis (e.g. gallstones, alcoholism, or hypertriglyceridemia).

Use of GLP-1 receptor agonists may be associated with acute gallbladder disease, see 7 **Error! Reference source not found.**, Gastrointestinal; Acute gallbladder disease)

Immune

Anaphylaxis and Serious Hypersensitivity Reactions:

ADLYXINE is contraindicated in patients with known hypersensitivity to this drug or its contents (see 2 CONTRAINDICATIONS).

In clinical trials, there have been cases of anaphylaxis determined to be related to ADLYXINE. Other serious hypersensitivity reactions, including angioedema also occurred (see 8 ADVERSE REACTIONS).

If a hypersensitivity reaction is suspected, the patient should discontinue ADLYXINE and seek immediate medical attention.

Patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist should be informed of and carefully monitored for allergic reactions, since it is unknown whether such patients will be predisposed to anaphylaxis with ADLYXINE.

Immunogenicity:

Patients may develop antibodies to lixisenatide following treatment with ADLYXINE. A pooled analysis of studies of lixisenatide-treated patients showed that 70% were antibody positive at Week 24 (see 8 ADVERSE REACTIONS). A higher incidence of allergic reactions and injection site reactions occurred in antibody positive patients. In the subset of patients with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed.

If a patient receiving ADLYXINE displays worsening glycemic control or failure to achieve targeted glycemic control, or if significant injection site reactions or allergic reactions occur, alternative antidiabetic therapy should be considered.

Monitoring and Laboratory Tests

Anticoagulation:

International normalized ratio (INR) should be monitored frequently when initiating or discontinuing ADLYXINE when co-administered with warfarin (see 9 DRUG INTERACTIONS).

Renal Function:

Assessment of renal function is recommended prior to initiation of ADLYXINE and periodically thereafter, as appropriate (see 7 WARNINGS AND PRECAUTIONS– Renal).

Renal

Therapeutic experience with ADLYXINE in patients with severe renal impairment is very limited, and there is no experience in patients with end stage renal disease or on dialysis. Therefore, use in these patients is not recommended.

Acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis or kidney transplantation, has been reported post-marketing in patients treated with GLP-1 receptor agonists (see 8 ADVERSE REACTIONS – Post-Market Adverse Reactions). Some of these events were reported in patients without known underlying renal disease. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration.

Since treatment with ADLYXINE may induce nausea, vomiting and diarrhea with transient hypovolemia, which may worsen renal function, renal function should be monitored when initiating or escalating doses of ADLYXINE especially in patients with renal impairment. Renal function should also be monitored in patients reporting severe gastrointestinal reactions (see 7 WARNINGS AND PRECAUTIONS

– Monitoring and Laboratory Tests).

7.1 Special Populations

7.1.1 Pregnant Women

ADLYXINE should not be used during pregnancy. Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). There are no adequate data from the use of ADLYXINE in pregnant women. The potential risk for humans is unknown. If a patient wishes to become pregnant, or pregnancy occurs, treatment with ADLYXINE should be discontinued.

7.1.2 Breast-feeding

ADLYXINE should not be used during breastfeeding. It is unknown if ADLYXINE is excreted in human milk. Lixisenatide was excreted in rat milk (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3 Pediatrics

ADYXINE should not be used in pediatric patients (< 18 years). The safety and effectiveness of ADLYXINE in patients below the age of 18 years have not been established.

7.1.4 Geriatrics

In Phase 2 and 3 controlled clinical studies of ADLYXINE including a specific study dedicated to non-frail diabetic older patients aged 70 years and over (see 14 CLINICAL TRIALS), a total of 2013 of the patients exposed to ADLYXINE were 65 years of age and over and 350 were 75 years of age and over. No overall differences were observed in safety or effectiveness between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In 9 placebo-controlled Phase 3 efficacy/safety studies, 2869 patients were exposed to ADLYXINE for a mean duration of exposure of 21. 7 weeks. Across the treatment arms, the mean age of patients was 56.1 years, 2.3% were 75 years or older and 48.2% were male. The population in these studies was 63.7% White, 2.6% Black or African American, 32.0% Asian; 18.9% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 8.1%. At baseline, 11.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 m2) in 95.3% of the pooled study populations (see 14 CLINICAL TRIALS).

In this data pool, the most frequently reported (≥5%) adverse events occurring more commonly in ADLYXINE treated patients than placebo were nausea (25.3%), vomiting (9.8%), hypoglycemia (13.7%) headache (8.5%), diarrhea (7.7%), and dizziness (6.7%).

The incidence of treatment discontinuation due to treatment-emergent adverse events was 7.2% for ADLYXINE compared to 3.2% in the placebo group. The most common treatment-emergent adverse events which led to treatment discontinuation in the ADLYXINE group were nausea (2.8%) and vomiting (1.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

summarizes common adverse events, excluding hypoglycemia, reported more commonly in ADLYXINE treated patients than placebo in 9 pooled Phase 3 placebo controlled efficacy/safety studies (main treatment period of 12-weeks for monotherapy and 24-weeks for other 8 studies).

Table 2 - Treatment-emergent Adverse Events Reported in ≥2% of ADLYXINE-treated Patients and Occurring More Frequently Compared to Placebo

	ADLYXINE n = 2869 (%)	**Placebo n = 1639 (%)**
Gastrointestinal disorders		
Nausea	725 (25.3)	99 (6.0)
Vomiting	282 (9.8)	30 (1.8)
Diarrhea	221 (7.7)	90 (5.5)
Dyspepsia	92 (3.2)	4 (0.2)
Constipation	79 (2.8)	30 (1.8)
Abdominal distension	64 (2.2)	14 (0.9)
Abdominal pain upper	62 (2.2)	14 (0.9)
General disorders and administration site conditions		
Asthenia	85 (3.0)	30 (1.8)
Fatigue	76 (2.6)	23 (1.4)
Infections and infestations		
Upper respiratory tract infection	96 (3.3)	42 (2.6)
Influenza	92 (3.2)	52 (3.2)
Urinary tract infection	59 (2.1)	29 (1.8)
Metabolism and nutrition disorders		
Decreased appetite	101 (3.5)	20 (1.2)
Musculoskeletal and connective tissue disorders		
Back pain	86 (3.0)	32 (2.0)
Nervous system disorders		
Headache	244 (8.5)	99 (6.0)
Dizziness	193 (6.7)	71 (4.3)
Tremor	64 (2.2)	18 (1.1)

**hypoglycemia is discussed separately*

Additional studies

The safety profile and adverse reactions reported in Table 2 above were consistent with those reported in 2 subsequent trials briefly described below.

One of these trials was conducted in elderly patients (N=350; mean age 74.2 years range 70-88 years) comparing ADLYXINE 20 mcg once daily vs. placebo, added on to standard of care.

The second trial (ELIXA) was a long-term cardiovascular outcomes trial (N=6068) which compared ADLYXINE 20 mcg once daily versus placebo, added on to standard of care, in high cardiovascular risk patients over a mean follow-up of 26 months.

Gastrointestinal adverse reactions:

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving ADLYXINE than placebo (placebo 18.4%, ADLYXINE 39.7%). More patients receiving ADLYXINE (4.3%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.5%). The severity of gastrointestinal adverse reactions in patients taking ADLYXINE was reported as “mild” in 64.2% of cases, “moderate” in 32.3% of cases, and “severe” in 3.5% of cases. Most of the adverse reactions occurred during the first 3 weeks of treatment.

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 <3.3 mmol/L, 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 2.0 mmol/L, or associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration if no plasma glucose was available.

Table **3** summarizes the incidence of symptomatic hypoglycemia and severe hypoglycemia by background anti-diabetic therapy based on seven placebo-controlled Phase 3 efficacy/safety studies.

Table 3 - Incidence (%) of Symptomatic Hypoglycemia and Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus during the 24-week Main Treatment Period

Background therapy	**Placebo**	**ADLYXINE**
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

Table 3 - Incidence (%) of Symptomatic Hypoglycemia and Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus during the 24-week Main Treatment Period

Background therapy	Placebo	ADLYXINE
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

Use with a sulfonylurea or basal insulin: Patients receiving ADLYXINE in combination with a sulfonylurea or basal insulin have an increased risk of hypoglycemia (see 7 WARNINGS AND PRECAUTIONS). Reduction of the dose of the sulfonylurea or basal insulin may be considered to reduce the risk of hypoglycemia (see 4 DOSAGE AND ADMINISTRATION).

Use with metformin and/or pioglitazone: A slightly higher rate of hypoglycemia was reported in patients treated with ADLYXINE in combination with metformin-alone or pioglitazone (with or without metformin).

Injection site reactions:

Injection site reactions (e.g. pain, pruritus and erythema) were reported more frequently in ADLYXINE-treated patients (4.0%) than placebo treated patients (1.8%).

Immunogenicity:

At Week 24, 70% of lixisenatide-treated patients were anti-drug antibody positive. 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 7 WARNINGS AND PRECAUTIONS).

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

No information regarding the presence of neutralizing antibodies is currently available. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of 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, it may be misleading to compare the incidence of antibodies to lixisenatide with the incidence of antibodies to other products.

The following subsections refer to larger safety data pools of Phase 2/3 controlled clinical trials.

Anaphylaxis and hypersensitivity reactions:

Anaphylaxis assessed by a clinical trial adjudication committee occurred in the clinical program with ADLYXINE (N=6413) at a rate of 0.2% or 16 cases per 10,000 patient years compared to 0.1% or 7 cases per 10,000 patient years with placebo (N=4820). The only cases of anaphylaxis adjudicated as possibly related to study drug occurred in ADLYXINE-treated patients.

Combined allergic reactions adjudicated as possibly related to study medication (including anaphylactic reaction, angioedema and urticaria) were reported more frequently in ADLYXINE-treated patients (0.4%) than placebo-treated patients (0.2%) (see 7 WARNINGS AND PRECAUTIONS).

Pancreatitis:

There were 21 cases of pancreatitis among 7354 ADLYXINE-treated patients and 14 cases among 6079 in comparator-treated patients (incidence rate of 21 vs. 17 per 10,000 patient-years, respectively). ADLYXINE 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.

8.3 Less Common Clinical Trial Adverse Reactions

The following is a list of less common treatment-emergent adverse events reported in the 9 Phase 3 placebo-controlled clinical trials. Adverse events reported in <2% and reported in greater frequency in ADLYXINE-treated patients than in placebo-treated patients are included in the listing.

Blood and lymphatic system disorders: neutropenia

Cardiac disorders: palpitations, supraventricular extrasystoles, tachycardia

Ear and labyrinth disorders: motion sickness, vertigo

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal discomfort, abdominal pain, dry mouth, dyspepsia, eructation, flatulence, frequent bowel movements, gastritis, gastroesophageal reflux disease, hyperchlorhydria, irritable bowel syndrome, regurgitation

General disorders and administration site conditions: chills, discomfort, face oedema, feeling abnormal, feeling cold, injection site erythema, injection site haematoma, injection site inflammation, injection site irritation, injection site macule, injection site nodule, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, malaise

Hepatobiliary disorders: acute gallbladder disease

Infections and infestations: gastroenteritis viral, nasopharyngitis

Immune system disorders: hypersensitivity

Musculoskeletal and connective tissue disorders: musculoskeletal pain, myalgia

Psychiatric disorders: anxiety, disorientation, food aversion, nervousness, restlessness

Respiratory, thoracic and mediastinal disorders: cough, nasal congestion, rhinorrhea, sneezing

Skin and subcutaneous tissue disorders: alopecia, dermatitis allergic, hyperhidrosis, rash, rash erythematous, rash maculo-papular, urticaria

Vascular disorders: flushing, hypertension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Increases in serum calcitonin:

In the ELIXA long-term cardiovascular outcomes trial, levels of serum calcitonin, a marker for thyroid C-cell proliferation, were elevated to ≥50 ng/L in 12 patients in the lixisenatide group (0.4%) and 2 patients in the placebo group (<0.1%). Similar elevations were seen a pool of Phase 2/3 studies, however reporting of calcitonin elevations in these trials was less consistently implemented. The clinical significance of these elevations is unclear.

8.5 Post-Market Adverse Reactions

The following serious and unexpected adverse events not previously listed in the clinical trial adverse reactions section of the Product Monograph have been reported. 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.

Renal:

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

When ADLYXINE is co-administered with sulfonylurea or basal insulin, there is a potential risk of hypoglycemia. A reduction of the concomitantly administered sulfonylurea or basal insulin may be necessary based on clinical experience (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION).

Co-administration of ADLYXINE with drugs that increase heart rate or prolong the PR interval should be undertaken with caution.

Delayed Gastric Emptying Effects on Oral Medications:

ADLYXINE delays gastric emptying which may reduce the rate of absorption of orally administered medications. Use caution when co administering ADLYXINE with oral medications that have a narrow therapeutic ratio or that require careful clinical monitoring. If such medications are to be administered with food, patients should be advised to take them with a meal or snack when ADLYXINE 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 ADLYXINE injection.

Patients taking oral contraceptives should be advised to take them at least 1 hour before ADLYXINE

administration or at least 11 hours after the dose of ADLYXINE.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Co-administered drug	Lixisenatide	Source of Evidence	Effect	Clinical comment
Acetaminophen 1000 mg, single dose	10 mcg, single dose	CT	No change in AUC_{last} and AUC_{inf} of acetaminophen whether administered before or after ADLYXINE. C_{max} decreased by 29% and 31% and median t_{max} was delayed by approximately 2 and 1.75 hours if acetaminophen was administered 1 or 4 hours after ADLYXINE.	No dose adjustment of acetaminophen is required when co-administered with ADLYXINE. Recommended to take acetaminophen 1 hour before ADLYXINE injection.

Table 4 - Established or Potential Drug-Drug Interactions

Co-administered drug	Lixisenatide	Source of Evidence	Effect	Clinical comment
Oral contraceptive 0.03 mg EE and 0.15 mg levonorgestrel, single dose	10 mcg, single dose	CT	Administration of oral contraceptives (ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after subcutaneous injection of lixisenatide 10 mcg, did not change the C_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$ and t_{max} of ethinyl estradiol and levonorgestrel. No change in AUC_{last} and AUC_{inf}, $t_{1/2}$ of EE or levonorgestrel if oral contraceptive was administered 1-4 hours after ADLYXINE. C_{max} of ethinyl estradiol and levonorgestrel decreased by 52% and 46% and t_{max} was delayed by 2 and 3 hours if oral contraceptive was administered 1 hour after ADLYXINE. C_{max} of ethinyl estradiol and levonorgestrel decreased by 39% and 20% and t_{max} was delayed by 1 hour each if oral contraceptive was administered 4 hours after ADLYXINE.	No dose adjustment of oral contraceptive is required when co-administered with ADLYXINE. It is recommended that oral contraceptives be administered at least 1 hour before or at least 11 hours after ADLYXINE administration.

Table 4 - Established or Potential Drug-Drug Interactions

Co-administered drug	Lixisenatide	Source of Evidence	Effect	Clinical comment
Atorvastatin 40 mg, repeated dosing	20 mcg, repeated dosing	CT	Co-administration with atorvastatin in the morning had no effect on $AUC_{0\text{-}24h}$ whereas C_{max} decreased by 31% and median t_{max} was delayed by 3.25 hours. If atorvastatin was administered in the evening, no such effect on t_{max} was observed while $AUC_{0\text{-}24h}$ and C_{max} were increased by 27% and 66%, respectively.	No dose adjustment of atorvastatin is required when co-administered with ADLYXINE. Recommended to take atorvastatin 1 hour before ADLYXINE injection.
Warfarin 25 mg, repeated dosing	20 mcg, repeated dosing	CT	No effects on S-warfarin AUC_{last} and AUC_{inf} or INR (International Normalized Ratio) while C_{max} was reduced by 19% and t_{max} was delayed by 7 hours.	No dose adjustment of warfarin is required when co-administered with ADLYXINE, but frequent INR monitoring is recommended at start or end of ADLYXINE treatment (see 7 WARNINGS AND PRECAUTIONS– Monitoring and Laboratory tests).
Digoxin 0.25 mg, repeated dosing	20 mcg, repeated dosing	CT	No change in $AUC_{0\text{-}24h}$ of digoxin whereas C_{max} was reduced by 26% and t_{max} of digoxin was delayed by 1.5 hours.	No dose adjustment of digoxin is required when co-administered with ADLYXINE.

Table 4 - Established or Potential Drug-Drug Interactions

Co-administered drug	Lixisenatide	Source of Evidence	Effect	Clinical comment
Ramipril 5 mg, repeated dosing	20 mcg, repeated dosing	CT	Increase in the AUC_{0-24h} of ramipril by 21% while the C_{max} was decreased by 63%. The AUC_{0-24h} and C_{max} of the active metabolite (ramiprilat) were not affected. T_{max} of ramipril and ramiprilat was delayed by 2.3 hours for Ramipril and 3 hours for Ramiprilat.	No dose adjustment of ramipril is required when co-administered with ADLYXINE.

Legend: CT = Clinical Trial; EE= ethinyl estradiol

Drugs that Increase Heart Rate:

ADLYXINE causes an increase in heart rate (see 7 WARNINGS AND PRECAUTIONS– Cardiovascular and 10 CLINICAL PHARMACOLOGY – Pharmacodynamics). The impact on heart rate of co-administration of ADLYXINE with other drugs that increase heart rate (e.g. sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of ADLYXINE with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation:

ADLYXINE causes an increase in the PR interval (see 7 WARNINGS AND PRECAUTIONS– Cardiovascular and 10 CLINICAL PHARMACOLOGY– Pharmacodynamics). The impact on the PR interval of co-administration of ADLYXINE with other drugs that prolong the PR interval (including, but not limited to, antiarrhythmics, calcium channel blockers, beta-adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of ADLYXINE with these drugs should be undertaken with caution.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lixisenatide is a selective GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas. After a meal, lixisenatide activates the following individual physiologic responses:

- Enhances insulin secretion by β-cells
- Delays gastric emptying.
- Suppresses glucagon secretion by α-cells.

Lixisenatide stimulates glucose dependent insulin secretion. In parallel, glucagon secretion is suppressed. Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

10.2 Pharmacodynamics

In a clinical pharmacology study in adults with type 2 diabetes mellitus, ADLYXINE, 20 mcg once daily reduced fasting plasma glucose level and postprandial blood glucose $AUC_{0\text{-}300min}$ compared to placebo (-1.88 mmol/L and -21.5 h mmol/L, 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.

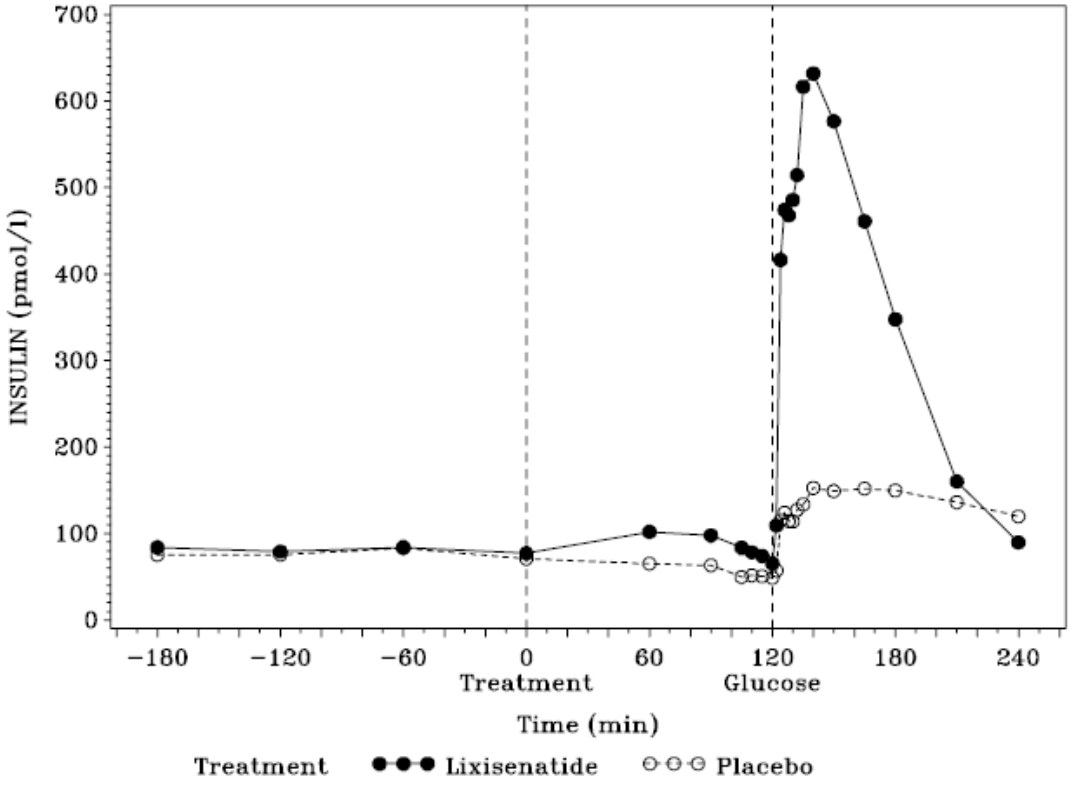
Glucagon secretion:

Treatment with ADLYXINE 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.

Insulin secretion:

As shown below (Figure 1), ADLYXINE restores the first-phase insulin response in patients with type 2 diabetes in a glucose-dependent manner by 6.6-fold (90% CI: 5.0, 8.7) and increases the second-phase insulin response by 3.0-fold (90% CI: 2.7, 3.3) compared with placebo as measured by AUC.

Figure 1: Mean insulin response during an IV glucose challenge after injection of 20 mcg ADLYXINE or placebo in patients with type 2 diabetes



Gastric emptying:

Following a standardized labelled test meal, ADLYXINE slows gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation. The delay of gastric emptying with ADLYXINE was maintained in an 8 week study in patients with type 2 diabetes mellitus.

Gallbladder Motility:

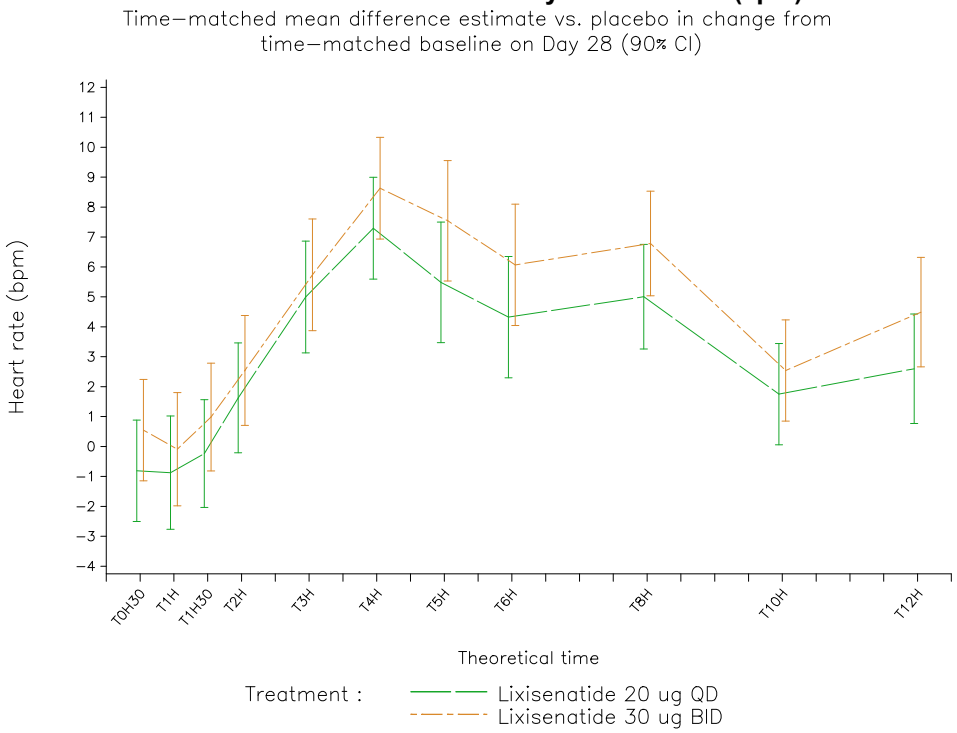
In a randomised, double-blind, placebo-controlled, crossover study, gallbladder motility was assessed in 24 healthy subjects who received single subcutaneous injections of 20 mcg ADLYXINE and placebo. ADLYXINE treatment caused statistically significant reductions in gall bladder ejection fraction (GBEF) in response to cholecystokinin-8, with mean differences from placebo in GBEF of 41.4% (95% CI: 28.6, 54.2) at 30 minutes and 45.8% (95% CI: 29.9, 61.7) at 60 minutes.

Cardiac electrophysiology:

A randomised, double-blind, double-dummy, repeated-dose, placebo-controlled, parallel group ECG assessment study was performed to assess the effect of lixisenatide at subcutaneous doses of 20 mcg once daily and a supratherapeutic dose of 30 mcg twice daily for 28 days in healthy subjects (N=60-62/treatment group). ECG assessments were performed at baseline and on day 28 of treatment.

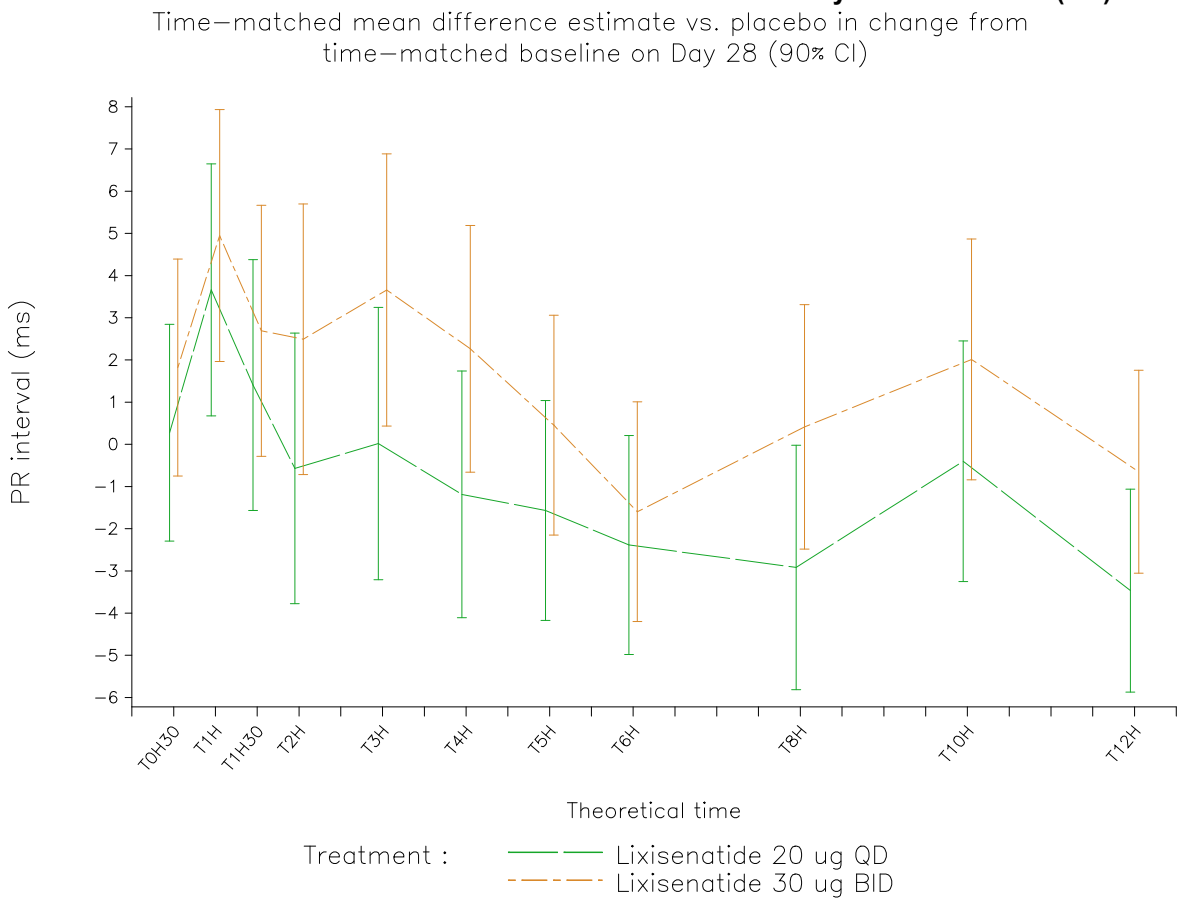
Heart Rate: ADLYXINE was associated with increases in heart rate. In the lixisenatide 20 mcg once daily group, the maximum difference from placebo in mean change from baseline heart rate was 7.3 bpm (90% CI: 5.6, 9.0) at the 4 h time point. In the lixisenatide 30 mcg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline heart rate was 8.6 bpm (90% CI: 7.0, 10.3) at 4 h. The 24 h time-averaged increase in mean heart rate was 3.9 (20 mcg once daily group), 5.8 bpm (30 mcg twice daily group), and 2.6 bpm (placebo) (see 7 WARNINGS AND PRECAUTIONS– Cardiovascular and 9 DRUG INTERACTIONS).

Figure 2:Time profile plot (mean and 90% CI) of pairwise comparisons versus placebo of time-matched mean difference estimates between T0h30 and T12h on Day 28 - Heart rate (bpm)



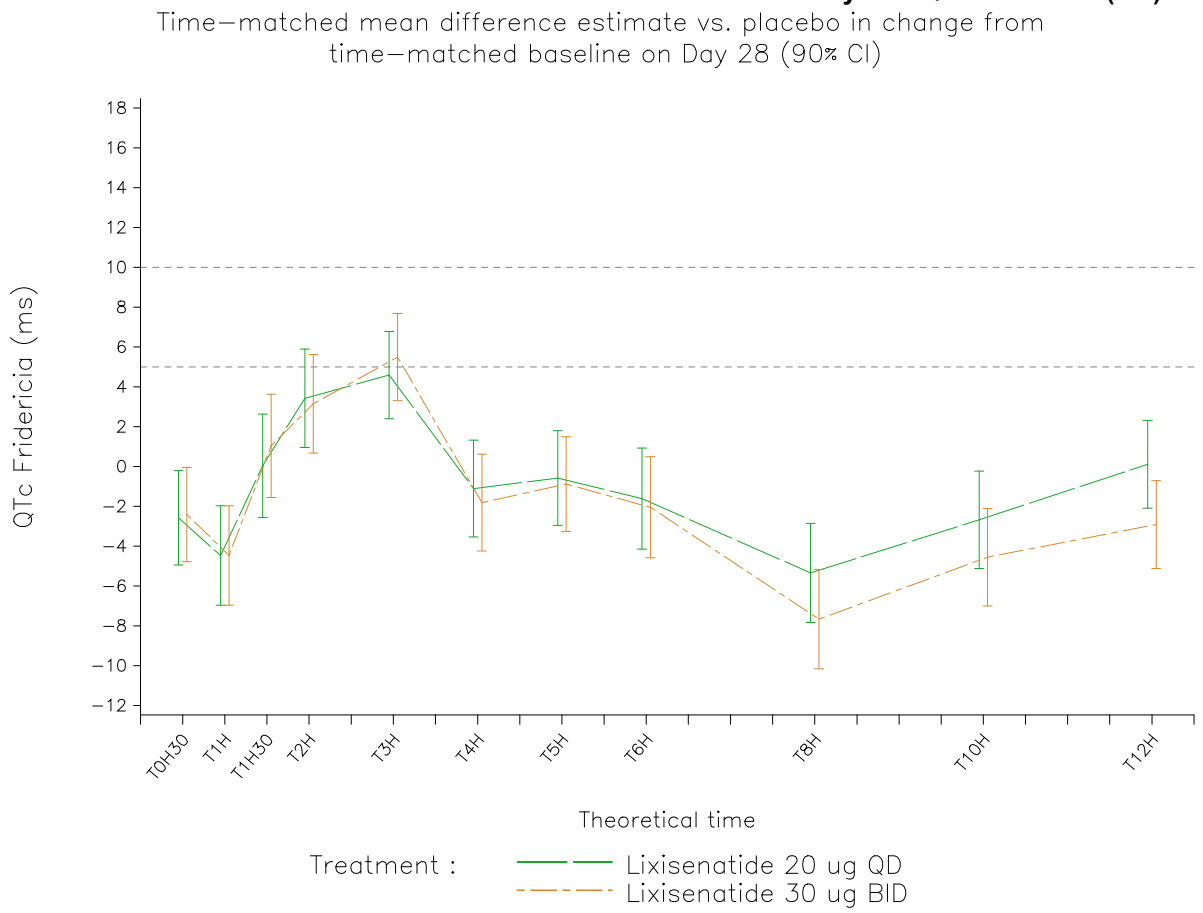
PR Interval: ADLYXINE resulted in PR interval prolongation. In the lixisenatide 20 mcg once daily group, the maximum difference from placebo in the mean change from baseline PR interval was 3.7 ms (90% CI: 0.6, 6.7) at the 1 h time point. In the lixisenatide 30 mcg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline PR interval was 5.0 ms (90% CI: 2.0, 8.0) at 1 h (see 7 WARNINGS AND PRECAUTIONS– Cardiovascular and 9 DRUG INTERACTIONS).

Figure 3: Time profile plot (mean and 90% CI) of pairwise comparisons versus placebo of time-matched mean difference estimates between T0h30 and T12h on Day 28 - PR interval (ms)



QTcF Interval: In the lixisenatide 20 mcg once daily group, the maximum difference from placebo in the mean change from baseline in QTcF interval (QTcF = QT/RR0.33) was 4.6 ms (90% CI: 2.3, 6.9) at the 3 h time point. In the lixisenatide 30 mcg twice daily (supratherapeutic dose) group, the maximum difference from placebo in mean change from baseline QTcF was 5.5 ms (90% CI: 3.2, 7.8) at 3 h. Caution should be observed in patients with risk factors for torsade de pointes (e.g. congenital long QT syndrome, cardiac disease, electrolyte abnormalities).

Figure 4: Time profile plot (mean and 90% CI) of pairwise comparisons versus placebo of time-matched mean difference estimates between T0h30 and T12h on Day 28 - QTc Fridericia (ms)



Ambulatory Heart Rate Monitoring: In an open-label, randomised, active-controlled, parallel group study of ADLYXINE in patients with type 2 diabetes not adequately controlled with insulin glargine, with or without metformin, ADLYXINE 20 mcg was administered for 8 weeks (N=46). Ambulatory heart rate monitoring performed on day 57/58 showed a mean change from baseline in daytime mean heart rate of 3.67 bpm (95% CI: 0.86, 6.48) and a mean change from baseline in nighttime mean heart rate of 2.20 bpm (95% CI: -0.72, 5.11) (see 7 WARNINGS AND PRECAUTIONS – Cardiovascular and 9 DRUG INTERACTIONS).

10.3 Pharmacokinetics

In anti-drug antibody (ADA) negative healthy subjects and ADA negative patients with type 2 diabetes mellitus, the pharmacokinetic profiles of lixisenatide were generally comparable.

Anti-drug antibody status:

In presence of ADA, mean exposure (AUC) to lixisenatide was approximately 5-fold increased, mean apparent clearance was decreased, and there was a corresponding increase in mean apparent half-life (Table 6), compared to pharmacokinetic parameters in absence of ADA (Table 5).

Table 5 - Summary of Lixisenatide Pharmacokinetic Parameters in ADA Negative Patients with type 2 diabetes mellitus after Repeated Dosing of 20 mcg QD at Steady State

	C_{max} (pg/mL)	T_{max} (h)	$t_{½}$ (h)	AUC[a] (pgh/mL)	CL (L/h)
Number	**9**	**9**	**9**	**9**	**9**
Geometric mean	175	1.3[b]	3.1	794	24.2
CV %	37	0.8 : 2.3[c]	65	40	38

[a] $AUC_{0:14\text{-}23:55h}$
[b] Median
[c] Min:Max
QD = once daily
CV = coefficient of variance

Table 6: Summary of Lixisenatide Pharmacokinetic Parameters in ADA Positive Patients with type 2 diabetes mellitus after Repeated Dosing of 20 mcg QD at Steady State

	C_{max} (pg/mL)	T_{max} (h)	$t_{½}$ (h)	AUC[a] (pg·h/mL)	CL/F (L/h)
Number	**10**	**10**	**10**	**10**	**10**
Geometric mean	562	2.8[b]	6.6	4437	4.5
CV %	75	0.8 : 20.0[c]	69	97	92

[a] $AUC_{0:14\text{-}23:55h}$
[b] Median
[c] Min:Max
QD = once daily
CV = coefficient of variance

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

After multiple dosing, exposure to lixisenatide was dose-proportional between doses of 10 and 20 mcg QD in healthy subjects, and approximately dose-proportional between doses of 5 and 30 mcg QD in ADA negative patients with type 2 diabetes mellitus.

After repeated dosing, no relevant accumulation of lixisenatide was observed in ADA negative patients with type 2 diabetes mellitus.

Distribution: Lixisenatide has a moderate level of binding (55%) to human proteins. The apparent volume of distribution (Vz/F) after subcutaneous administration of lixisenatide is approximately 100L.

Metabolism: As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent proteolytic degradation, resulting in smaller peptides and amino acids.

Elimination: 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.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of ADLYXINE have not been established in patients younger than 18 years of age, therefore ADLYXINE is not indicated in pediatric patients.
- **Geriatrics:** ADLYXINE should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out.
- **Sex:** Gender does not affect the pharmacokinetics of lixisenatide based on a population pharmacokinetic data analysis. The geometric mean exposure in females was 13% higher than in males and is not considered to be clinically relevant.
- **Genetic Polymorphism:** Being a peptide, lixisenatide is subject to standard proteolytic processes. Therefore, genetic polymorphism is not expected to have a relevant effect on the pharmacokinetics of lixisenatide.
- **Ethnic Origin:** Race had no clinically relevant effect on the pharmacokinetics of lixisenatide based on the results of pharmacokinetic studies in Caucasian, Japanese and Chinese subjects. The geometric mean exposure in Caucasian patients was 12% lower compared to Asians and is not considered to be clinically relevant.
- **Hepatic Insufficiency:** No pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.
- **Renal Insufficiency:** Compared to healthy subjects (N=4; CL_{cr} greater than or equal to 90 mL/min), plasma C_{max} of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild (N=9), moderate (N=11), and severe (N=8) renal impairment (CL_{cr} 60-89, 30-59 and 15-29 mL/min), respectively; plasma AUC_{inf} was increased by approximately 46%, 51% and 87% with mild, moderate and severe renal impairment, respectively.

  Therapeutic experience with ADLYXINE in patients with severe renal impairment is extremely limited, and there is no experience in patients with end stage renal disease or on dialysis. Therefore, use in these patients is not recommended.

- **Body Weight:** The population pharmacokinetic analysis showed that lixisenatide exposure decreased with increasing body weight in a nonlinear manner, with greater changes for low body weights.

11 STORAGE, STABILITY AND DISPOSAL

Unopened ADLYXINE pen should be stored in a refrigerator, between 2°C-8°C. Do not freeze. Keep the pen in the original package to protect it from light.

The opened pen may be stored at up to 30°C for up to 14 days. Do not store with needle attached. Replace the pen cap after each use to protect from light.

Discard the pen 14 days after first use, or if exposed to excessive heat or freezing.

12 SPECIAL HANDLING INSTRUCTIONS

The pen cap should be replaced on the pen after each use in order to protect from light. The pen

should not be stored with a needle attached.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

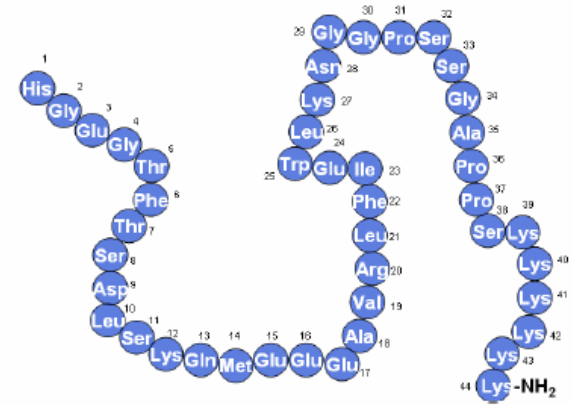
Drug Substance

Proper name: lixisenatide

Chemical name: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys-NH_2

Molecular formula and molecular mass: $C_{215}H_{347}N_{61}O_{65}S$
4858.5 (average)

Structural formula:



Lixisenatide is a novel human glucagon-like peptide-1 receptor (GLP-1R) agonist for the treatment of type 2 diabetes mellitus. The structure of lixisenatide was based on exendin-4 (1-39), which was modified by adding six Lysine residues C-terminally. These modifications enable the product to withstand physiological degradation by dipeptidyl peptidase IV

Physicochemical properties:

Appearance:	Amorphous, hygroscopic, white to off-white powder
Solubility at 25°C:	Citrate buffer, pH from 2 to 10: ~6 mg/mL, at all pH values Phosphate buffer, pH from 2 to 9: ~6 mg/mL, at all pH values

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%M/F)
Add-on Combination Therapy with Metformin					
EFC10743 GetGoal-F1	Randomized, double-blind, placebo-controlled, parallel-group study	ADLYXINE 20 mcg QD, sc 2-step initiation** 1-step initiation* Placebo QD, sc Main treatment period: 24 weeks Extension period: variable	One step: 161 Two step: 161 Placebo: 162	56.1 (24-79)	45/55
EFC6014 GetGoal-M	Randomized, double-blind, placebo-controlled, 4-arm, parallel-group study	Morning (Breakfast) ADLYXINE 20 mcg QD, sc Evening (Dinner) ADLYXINE 20 mcg QD, sc Placebo morning or evening, sc Main treatment: 24 weeks Extension: up to 76 weeks	Morning: 255 Evening: 255 Placebo: 170	54.7 (23-87)	43/57

Table 7 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%M/F)
Add-on Combination Therapy with Pioglitazone (+/- Metformin)					
EFC6017 GetGoal-P	Randomized, double-blind, placebo-controlled, 2-arm parallel-group study	ADLYXINE 20 mcg QD (2-step), sc Placebo QD, sc Main treatment: 24 weeks Extension: up to 76 weeks	Lixisenatide: 323 Placebo: 161	55.8 (26-82)	52/48
Add-on Combination Therapy with Sulfonylurea (+/- Metformin)					
EFC6015 GetGoal-S	Randomized, double-blind, placebo-controlled, 2-arm, parallel-group study	ADLYXINE 20 mcg QD, sc Placebo QD, sc Main treatment: 24 weeks Extension: up to 76 weeks	Lixisenatide: 573 Placebo: 286	57.2 (20-79)	51/49
Add-On Combination Therapy with Basal Insulin (+/- Metformin)					
EFC6016 GetGoal-L	Randomized, double-blind, placebo-controlled, 2-arm parallel-group study	ADLYXINE 20 mcg QD, sc Placebo QD, sc Main treatment: 24 weeks	Lixisenatide: 329 Placebo: 167	57.2 (29-81)	46/54

Table 7 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%M/F)
Studies in Special Populations					
EFC12703 GetGoal-O	Randomized, placebo-controlled, 2-arm parallel-group, multinational, multicenter study in elderly patients	ADLYXINE 20 mcg QD (1-step), sc Placebo QD, sc Main treatment: 24 weeks	Lixisenatide: 176 Placebo: 174	74.2 (70-88)	52/48
EFC11319 ELIXA	Randomized, placebo-controlled, double-blind, parallel-group study in high cardiovascular risk patients	ADLYXINE 20 mcg QD (1-step), sc Placebo QD, sc Main treatment: minimum 10 months	Lixisenatide: 3034 Placebo: 3034	60.3 (30-93)	69/31

*1-step initiation: 10 mcg QD for 2 weeks, then maintenance dose of 20 mcg QD)
**2-step initiation: 10 mcg QD for 1 week, then 15 mcg QD for 1 week, then maintenance dose of 20 mcg QD – only the 1-step titration regimen is approved.
sc = subcutaneous; QD = once daily

14.2 Study Results

Add-on therapy with metformin

A total of 1159 subjects with type 2 diabetes mellitus and inadequate glycemic control despite a stable dose of metformin (minimum 1500 mg/day) for at least 3 months prior to screening were evaluated for efficacy in two 24-week plus long term extension trials of ADLYXINE vs. placebo in combination with metformin.

In Study EFC10743, ADLYXINE and placebo were administered in 1-step and 2-step dose initiation regimens and study drug was administered 1 hour before the morning meal. In Study EFC6014, only a 2-step dose initiation regimen was evaluated and ADLYXINE or placebo were administered 1 hour before either the morning or evening meal. In each of the 2 studies, efficacy analyses were conducted for ADLYXINE vs. the combined placebo group (i.e. in EFC10743, placebo patients in the 1-step and 2-step titration regimens were combined and in EFC6014, placebo patients in the morning and evening injection groups were combined). Only the 1-step dose initiation regimen is approved.

In both studies, approximately 14% of randomized patients were aged ≥65 to <75 years, and 2% were aged ≥75 years. Mean baseline body mass index (BMI) was approximately 33 kg/m^2, approximately 89-90% of patients were Caucasian/White, with lesser representation of Asian (7%), Black (2%), and other

races (1%). In the studies, mean duration of diabetes at screening was approximately 6 years.

For the primary endpoint, both studies showed statistically significant reductions in HbA1c compared to placebo, at the end of the main 24-week treatment period (Table 8).

Table 8 - Placebo-controlled Studies in Combination with Metformin (24-week results)

	EFC10743 / GetGoal-F1			**EFC6014 / GetGoal-M**		
Background therapy	Metformin			Metformin		
Randomized groups	ADLYXINE		Placebo	ADLYXINE		Placebo
	1-step dose initiation	2-step dose initiation		Morning	Evening	
Mean HbA1c (%)						
N (mITT)	156	152	158	244	239	164
Baseline	7.99	8.12	8.03	8.07	8.07	8.02
LS mean change from baseline (LOCF)	-0.92	-0.83	-0.42	-0.87	-0.75	-0.38
LS mean difference vs. placebo (95% CI)	-0.49‡ (-0.670, -0.317)	-0.41‡ (-0.583, -0.232)		-0.48‡ (-0.657, -0.312)	-0.37‡ (-0.540, -0.193)	
Patients (%) achieving HbA1c <7.0%#						
Responders	47.4	42.1	24.1	43.0	40.6	22.0
FPG (mmol/L)						

Table 8 - Placebo-controlled Studies in Combination with Metformin (24-week results)

	EFC10743 / GetGoal-F1			EFC6014 / GetGoal-M		
Background therapy	Metformin			Metformin		
Randomized groups	ADLYXINE		Placebo	ADLYXINE		Placebo
	1-step dose initiation	2-step dose initiation		Morning	Evening	
N (mITT)	158	160	158	253	255	170
Baseline	9.55	9.52	9.46	9.46	9.28	9.51
LS mean change from baseline (LOCF)	-0.53	-0.56	0.11	-1.19	-0.81	-0.25
LS mean difference vs. placebo (95% CI)	-0.65‡ (-1.019, -0.275)	-0.67‡ (-1.035, -0.301)		-0.94‡ (-1.329, -0.559)	-0.56† (-0.944, -0.173)	
Mean body weight (kg)						
N (mITT)	158	155	158	248	249	168
Baseline	90.30	88.08	87.86	90.14	89.01	90.40
LS mean change from baseline (LOCF)	-2.63	-2.68	-1.63	-2.01	-2.02	-1.64
LS mean difference vs. placebo (95% CI)	-1.00† (-1.687, -0.317)	-1.05† (-1.727, -0.371)		-0.38 NS (-0.995, 0.239)	-0.39 NS (-1.006, 0.230)	

Table 8 - Placebo-controlled Studies in Combination with Metformin (24-week results)

	EFC10743 / GetGoal-F1			EFC6014 / GetGoal-M		
Background therapy	Metformin			Metformin		
Randomized groups	ADLYXINE		Placebo	ADLYXINE		Placebo
	1-step dose initiation	2-step dose initiation		Morning	Evening	

1-step initiation = 10 mcg QD for 2 weeks, then maintenance dose of 20 mcg QD
2-step initiation = 10 mcg QD for 1 week, then 15 mcg QD for 1 week, then maintenance dose of 20 mcg QD
QD = once daily
Only the 1-step titration regimen is approved.
LOCF = Last observation carried forward; mITT = modified intent-to-treat, consists of all patients who were randomized, received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.
† = $p<0.01$ treatment vs. placebo; ‡ = $p<0.001$ treatment vs. placebo
NS = not statistically significant
# = included for descriptive purposes only

Add-on Therapy with Pioglitazone

In Study EFC6017, patients with inadequate glycemic control on a stable dose of pioglitazone, with or without metformin, were randomised (2:1) to receive 24-week double-blind treatment with either lixisenatide or placebo.

Approximately 16% of randomized patients were aged ≥65 to <75 years, and 2% were aged ≥75 years. Mean BMI was approximately 33.9 kg/m^2, 84% of patients were Caucasian/White, with lesser representation of Asian (5%) and Black (5%). The mean duration of diabetes at screening was 8.1 years.

For the primary endpoint, the addition of lixisenatide, with or without metformin, to pioglitazone provided statistically significant improvements in HbA1c after 24 weeks of treatment compared to placebo (Table 9).

Table 9 - 24-week Placebo-controlled Study of ADLYXINE as Add-on to Pioglitazone (+/- metformin)

	EFC6017 / GetGoal-P	
	ADLYXINE	**Placebo**
Background therapy	Pioglitazone +/- metformin	
Mean HbA1c (%)		
N (mITT)	308	148
Baseline	8.08	8.05
LS mean change from baseline	-0.90	-0.34
LS mean difference vs. placebo	-0.56‡	
(95% CI)	(-0.731, -0.386)	
Patients (%) achieving HbA1c <7%#		
Responders	52.3	26.4
FPG (mmol/L)		
N (mITT)	317	159
Baseline	9.14	9.12
LS mean change from baseline	-1.16	-0.32
LS mean difference vs. placebo	-0.84‡	
(95% CI)	(-1.209, -0.467)	
Body weight (kg)		
N (mITT)	315	157
Baseline	92.83	97.03
LS mean change from baseline	-0.21	0.21
LS mean difference vs. placebo	-0.41 NS	
(95% CI)	(-1.031, 0.201)	

LOCF = Last observation carried forward; mITT = modified intent-to-treat, consists of all patients who were randomized, received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

‡ = $p<0.001$ treatment vs. placebo

NS = not statistically significant

= included for descriptive purposes only

Add-on Therapy with a Sulfonylurea

Study EFC6015 was a 24-week trial of patients inadequately controlled on a stable dose of sulfonylurea, with or without metformin. Patients were randomised (2:1) to receive either lixisenatide or placebo.

Approximately 21% of randomized patients were aged ≥65 to <75 years, and 3% were aged ≥75 years. Mean BMI was approximately 30.2 kg/m^2, 52% of patients were Caucasian/White, 45% were Asian and 3% were Black. The mean duration of diabetes at screening was 9.4 years.

For the primary endpoint, the addition of lixisenatide to a sulfonylurea, with or without metformin, provided statistically significant improvements in HbA1c after 24 weeks of treatment compared to placebo (Table 10).

Table 10 - 24-week Placebo-controlled Study of ADLYXINE as Add-on to Sulfonylurea (+/- metformin)

	EFC6015 / GetGoal-S	
	ADLYXINE	**Placebo**
Background therapy	Sulfonylurea +/- metformin	
Mean HbA1c (%)		
N (mITT)	544	274
Baseline	8.28	8.22
LS mean change from baseline (LOCF)	-0.85	-0.10
LS mean difference vs. placebo	-0.74‡	
(95% CI)	(-0.867, -0.621)	
Patients (%) achieving HbA1c <7%#		
Responders	36.4	13.5
FPG (mmol/L)		
N (mITT	564	283
Baseline	9.67	9.29
LS mean change from baseline (LOCF)	-0.99	-0.36
LS mean difference vs. placebo	-0.63‡	
(95% CI)	(-0.919, -0.346)	
Body weight (kg)		

Table 10 - 24-week Placebo-controlled Study of ADLYXINE as Add-on to Sulfonylurea (+/- metformin)

	EFC6015 / GetGoal-S	
	ADLYXINE	**Placebo**
N (mITT)	554	278
Baseline	82.58	84.52
LS mean change from baseline (LOCF)	-1.76	-0.93
LS mean difference vs. placebo	-0.84‡	
(95% CI)	(-1.250, -0.421)	

LOCF = Last observation carried forward; mITT = modified intent-to-treat consists of all patients who were randomized, received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.
‡ = $p < 0.001$ treatment vs. placebo
# = included for descriptive purposes only

Add-on combination therapy with a basal insulin

Study EFC6016 compared ADLYXINE, given with a basal insulin alone, or with a combination of a basal insulin and metformin, to placebo. Patients not adequately controlled on a stable dose of basal insulin with or without metformin were randomized (2:1) to receive either ADLYXINE or placebo for the 24-week main treatment period.

Approximately 19% of randomized patients were aged ≥65 to <75 years, and 3% were aged ≥75 years. Mean BMI was approximately 32.1 kg/m^2, 78% of patients were Caucasian/White, 17% were Asian and 4% were Black. The mean duration of diabetes at screening was 12.5 years.

For the primary endpoint, the addition of ADLYXINE to basal insulin provided a statistically significant improvement in HbA1c after 24 weeks of treatment, compared to placebo (Table 11).

Table 11 - 24-week Placebo-controlled Study of ADLYXINE as Add-on Therapy to Basal Insulin (+/- Metformin)

	EFC6016 / GetGoal-L	
	ADLYXINE	**Placebo**
Background therapy	Basal insulin with or without metformin	
Mean HbA1c (%)		

Table 11 - 24-week Placebo-controlled Study of ADLYXINE as Add-on Therapy to Basal Insulin (+/- Metformin)

	EFC6016 / GetGoal-L	
	ADLYXINE	**Placebo**
N (mITT)	304	158
Baseline	8.39	8.38
LS mean change from baseline (LOCF)	-0.74	-0.38
LS mean difference vs. placebo	-0.36‡	
(95% CI)	(-0.550, -0.174)	
Patients (%) achieving HbA1c <7%#		
Responders	28.3	12.0
FPG (mmol/L)		
N (mITT)	317	163
Baseline	8.11	8.03
LS mean change from baseline (LOCF)	-0.63	-0.55
LS mean difference vs. placebo	-0.08 NS	
(95% CI)	(-0.590, 0.430)	
Body weight (kg)		
N (mITT)	311	161
Baseline	87.39	89.11
LS mean change from baseline (LOCF)	-1.80	-0.52
LS mean difference vs. placebo	-1.28 NS	
(95% CI)	(-1.803, -0.747)	

LOCF = Last observation carried forward; mITT = modified intent-to-treat consists of all patients who were randomized, received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

‡ = p<0.001 treatment vs. placebo

NS = not statistically significant/hierarchical testing procedure stopped earlier

= included for descriptive purposes only

Studies in Special Populations

Patients aged ≥70 years

In Study EFC12703, the efficacy and safety of lixisenatide, administered before breakfast, in patients with type 2 diabetes mellitus aged ≥70 years was evaluated in a double-blind, placebo-controlled study of 24 weeks duration. Frail patients, including patients at risk for malnutrition and patients with moderate to severe cognitive impairment, were excluded.

A total of 350 patients were randomized 1:1. Overall, 37% of the patients were ≥75 years old and 11% were >80 years, approximately 71% were Caucasian/White, 5% were Asian, and 23% were described as Other. Mean BMI was 30.0 kg/m^2, mean duration of diabetes was 14.1 years, and 31% of patients had moderate renal impairment. At baseline, approximately one third of patients were being treated with basal insulin with or without oral antidiabetic drugs, one third with a combination of oral antidiabetic drugs including sulfonylurea, and one third with a combination of oral antidiabetic drugs excluding sulfonylurea.

For the primary endpoint, compared to placebo, treatment with ADLYXINE resulted in a statistically significant reduction in HbA1c at Week 24 (Table 12).

Table 12 - 24-week Placebo-Controlled Study in Patients Aged >70 Years on Stable Dose(s) of Oral Antidiabetic Drugs (OAD) and/or Basal Insulin

	EFC12703 / GetGoal-O	
	ADLYXINE	**Placebo**
Background therapy	OAD as background therapy with or without basal insulin[+]	
Mean HbA1c (%)		
N (mITT)	172	172
Baseline	8.03	8.05
LS mean change from baseline (LOCF)	-0.57	0.06
LS mean difference vs. placebo	-0.64[‡]	
(95% CI)	(-0.810, -0.464)	
Patients (%) achieving HbA1c <7%[#]		
Responders	36.6	14.0
FPG (mmol/L)		
N (mITT)	171	168
Baseline	8.83	8.85
LS mean change from baseline (LOCF)	-0.30	0.01
LS mean difference vs. placebo	-0.31 NS	
(95% CI)	(-0.828, 0.204)	

Table 12 - 24-week Placebo-Controlled Study in Patients Aged >70 Years on Stable Dose(s) of Oral Antidiabetic Drugs (OAD) and/or Basal Insulin

	EFC12703 / GetGoal-O	
	ADLYXINE	**Placebo**
Body weight (kg)		
N (mITT)	174	173
Baseline	80.76	80.24
LS mean change from baseline (LOCF)	-1.47	-0.16
LS mean difference vs. placebo	-1.32‡	
(95% CI)	(-1.862, -0.769)	

+ sulfonylurea or glinides were not used with basal insulin as background therapy
LOCF = Last observation carried forward; mITT = modified intent-to-treat consists of all patients who were randomized, received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures
‡ = p<0.001 treatment vs. placebo
NS = not statistically significant
# = included for descriptive purposes only

Cardiovascular Outcomes Study

The ELIXA trial was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome event. The primary composite efficacy endpoint was the time to the first occurrence of a major cardiovascular event (MACE) defined as any of the following events positively adjudicated by the Cardiovascular Events Adjudication Committee:

- cardiovascular death,
- non-fatal myocardial infarction,
- non-fatal stroke, or
- hospitalization for unstable angina.

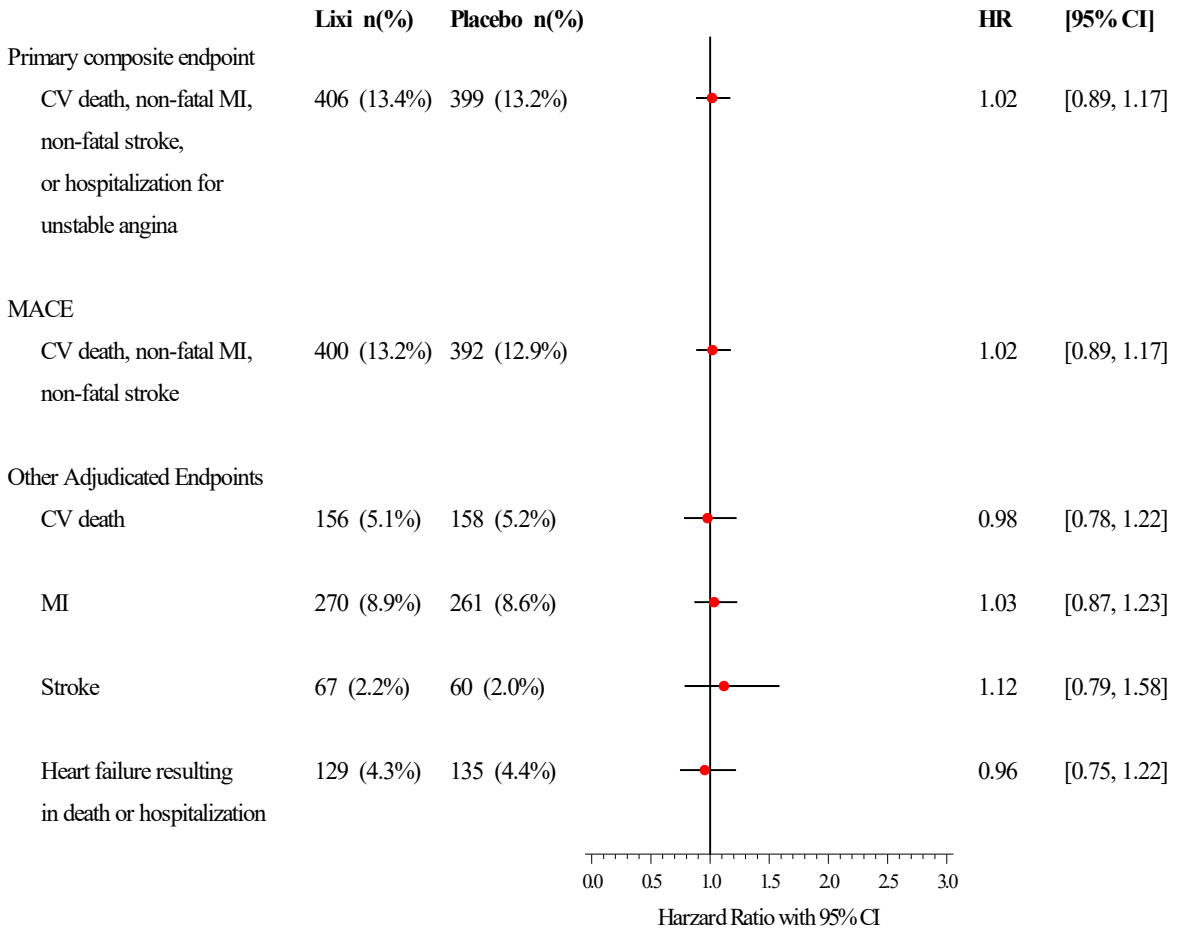
The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio comparing ADLYXINE to placebo.

Overall, 6068 patients were randomized 1:1 to either placebo or lixisenatide 20 mcg (following a starting dose of 10 mcg during the first 2 weeks). The demographics and baseline characteristics were well balanced between treatments (see Table 7). Approximately 75% of the patients 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 23.2% had an estimated GFR less than 60 mL/min/1.73 m^2. Use of cardiovascular medications at baseline was similar between treatments; platelet aggregation inhibitors (acetylsalicylic acid 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 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 lixisenatide and placebo group, respectively. Median treatment duration was 22.4 months in the lixisenatide 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 efficacy endpoint and other adjudicated endpoints are shown in Figure 5. The hazard ratio (HR) for lixisenatide 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 excluded a risk margin larger than 1.3, thus demonstrating non-inferiority to placebo. Superiority to placebo was not demonstrated. Hazard ratios for the other adjudicated endpoints were not statistically significant.

Figure 5: Forest plot: analyses of adjudicated cardiovascular outcomes - ITT population



CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio, CI: confidence interval.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

NON-CLINICAL PHARMACODYNAMICS

Lixisenatide is a peptide and has high and specific affinity for the GLP-1 receptor in vitro. Results of the pharmacology evaluation are consistent with lixisenatide being an agonist. Chronic administration of lixisenatide in rodent models for type 2 diabetes showed decreased concentrations of fasting blood glucose, as well as percentage glycated hemoglobin, indicative of the prevention of the progressive development of diabetes in these models.

NON-CLINICAL PHARMACOKINETICS

Systemic exposure (Cmax and AUC) generally increased approximately dose proportionally in mice, rats, and dogs after a single lixisenatide dose. After repeated daily sc dosing, lixisenatide induced an immunogenic response, with antidrug antibodies (ADA) detectable in all species. Consequently AUC, and to a lesser extent Cmax, increased more than dose proportionally. The accumulation due to antibody binding with repeated dosing differs among species (rat>mice>dogs>human).

In rats, lixisenatide was distributed to kidneys, lung, pancreas, and adrenals. Transfer of intact lixisenatide to brain, across the placenta, and via the milk was limited. Lixisenatide was extensively degraded in vitro, presumably by proteases, with a total of 28 metabolites identified, and all were degraded peptides of lixisenatide and excreted in urine and feces.

Safety margins versus clinical exposure were calculated using results of ADA negative animal exposure compared to clinical ADA positive exposure (ADA positive AUC of 7.25 ng h/mL after administration of the recommended 20 mcg/day dose). The rationale for using exposure data from ADA negative animals in the calculation of safety margins is that it is not known what fraction of total (antibody bound and unbound) lixisenatide exposure is active in vivo and furthermore, while most animals develop antibodies, some do not. Margins based on ADA positive animals and/or ADA negative patients are much higher.

Acute Toxicity:

A single dose of 500, 5000, and 100 mcg/kg iv or 500, 5000, and 200 mcg/kg sc was tolerated without mortality in mice, rats, and dogs, respectively.

Repeated Dose Toxicity:

The repeated dose toxicity of lixisenatide after sc twice daily (8 h apart) administration was evaluated in mice, rats, and dogs for up to 13, 26, and 52 weeks, respectively.

Changes in body weight/body weight gain in mice and rats and clinical signs were generally mild. No target organs relevant to human safety were identified and lixisenatide was tolerated in mice and rats at doses up to 4000 mcg/kg/day (lixisenatide AUC values >47 times the mean clinical exposure of 7.25 ng h/mL).

In dogs, reductions in food consumption and body weight loss were dose limiting. Initial dose escalation attenuated the effects of lixisenatide on body weight and food consumption. Using dose escalation, administration of doses up to 2000 mcg/kg/day for 52 weeks was possible. There were no target organs in females. In males, microscopic changes were noted in testes and epididymes in the 13 week study at 200 and 500 mcg/kg/day and in the 52 week study at 400 and 2000 mcg/kg/day. The changes in the testes included moderate to severe hypospermatogenesis in seminiferous tubules and epididymal dilation, degeneration, and oligospermia, or aspermia and were not present after 4 weeks without treatment at the end of the 13 week study. The changes in testes and epididymes occurred at very high multiples of human exposure (>140 times). The large margins to clinical exposure for effects on testes/epididymes in the dogs, as well as a mechanistic study showing species difference in GLP-1receptor expressions, indicate a very low risk for effects to male patients with the clinical use of lixisenatide

Carcinogenicity: Carcinogenicity studies were conducted in mice and rats given sc lixisenatide doses of 40, 200, and 1000 mcg/kg BID for 2 years. In mice, lixisenatide resulted in thyroid gland C-cell adenomas in males at 1000 mcg/kg BID and increased incidences of thyroid focal C-cell hyperplasia in males at 200 mcg/kg BID and males and females given 1000 mcg/kg BID. In rats, there were non dose-dependent increased incidences of thyroid C-cell focal hyperplasia and adenomas at all dose levels and C-cell carcinomas at 200 and 1000 mcg/kg BID in both sexes.

A no-effect dose level for increased thyroid hyperplasia and C-cell adenomas was not identified in rats. Systemic exposure at the low dose in rats was >9-fold when comparing mean AUC values in rats to clinical exposure, while that at the higher doses where C-cell carcinomas were observed was ≥35-fold. In mice, lixisenatide-related thyroid C-cell adenomas were confined to the high dose males given 1000 mcg/kg BID, at which exposure was 128 times that in patients. The exposure margin at the 200 mcg/kg no effect dose level for tumors was 26-fold. Increased incidences of thyroid C-cell hyperplasia were seen at 200 (males only) and 1000 mcg/kg BID, with mouse/human margins at the no effect dose level of 40 mcg/kg BID calculated as 4-fold.

Genotoxicity:

Lixisenatide was not mutagenic or clastogenic in vitro in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), *in vitro* human lymphocyte chromosome aberration, in vivo mouse bone marrow micronucleus).

Reproductive and Developmental Toxicology:

Impairment of Fertility

Studies in which male and female rats received twice daily subcutaneous doses of 2, 29, or 414 mcg/kg/day 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/day, or approximately 300 times the clinical systemic exposure at 20 mcg/day based on plasma AUC.

Embryo fetal development

Lixisenatide transfer across the placenta was limited and effects on embryo fetal development in rats and rabbits were noted in the presence of maternal toxicity. Body weight loss and reduced food consumption may have contributed to the embryo fetal toxicity, but a direct effect cannot be excluded. A relationship of toxicity to the dams on skeletal ossification and fetal growth is generally accepted; however, the correlation to visceral and external malformations is less well supported.

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg (5, 70, or 1000 mcg/kg/day) from gestation day (GD) 6 to 17 (organogenesis), maternal toxicity was noted at all doses, which consisted of clinical signs and initially dose-dependent decreases in body weight and reduced food consumption. Fetuses showed a dose related trend of retarded growth and retarded ossification. All doses led to single cases of fetal malformations: one microphthalmia (5 mcg/kg/day), one anophthalmia and one diaphragmatic hernia (one fetus each at 70 mcg/kg/day), and similar multiple skeletal malformations in one retarded fetus of each dose group. Thus, the NOAEL for embryo fetal toxicity was less than 5 mcg/kg/day (AUC < clinical exposure).

In rabbits, there were two embryo fetal development studies. In the high dose study, lixisenatide was administered sc at 5, 50, and 500 mcg/kg/day twice daily (approximately 8 h apart) from GD 6 to 18, while in the follow up study, doses were 0.3, 2, and 5 mcg/kg/day. Lixisenatide treatment at ≥2 mcg/kg/day resulted in decreased motor activity, piloerection, decreased food and water consumption, and initial decreases body weight followed by decreased body weight gain. There was a slight increase in postimplantation loss with a related decrease in the number of live fetuses at 500 mcg/kg/day. There was an increase at fetal malformations at ≥5 mcg/kg/day (4-times clinical exposure). In the high dose study, there were 5 cases of multiple malformations (2 at 5 mcg/kg/day, 2 at 50 mcg/kg/day, and 1 at 500 mcg/kg/day), as well as single malformations at all doses. There was also a tendency to dose dependent increases in fetuses showing anomalies of the sternebrae, as well as retarded ossification. The NOAEL for maternal toxicity in rabbit was 0.3 mcg/kg/day and for embryo-fetal development was 2 mcg/kg/day, and at these doses, AUC values were < clinical exposure and 2 times clinical exposure, respectively.

Peri and postnatal development

Lixisenatide was administered to time mated female rats (F0 generation) sc at 4, 40, and 400 mcg/kg/day (2, 20, and 200 mcg/kg/day BID) from GD 6 to lactation day 21. Clinical signs in dams, initial body weight loss with reduced body weight throughout dosing and reduced food consumption, were seen at all dose levels. Pup mortality was slightly increased and there were severely growth delayed pups with multiple skeletal malformations at 400 mcg/kg/day. The number of pups/litter that showed insufficient suckling increased slightly and coat growth showed a slight delay at 40 and 400 mcg/kg/day, but there were no other effects on developmental landmarks, sensory function, motor development, memory, learning, and reproductive function of the F1 generation. The NOAEL for effects in the F0 dams was not identified (<4 mcg/kg/day), while the NOAEL for toxicity in F1 animals was 4 mcg/kg/day. Based on systemic exposure values in pregnant rats extrapolated from toxicokinetic data in the pivotal embryo-fetal development study, exposure at the 400 mcg/kg/day dose where malformations were seen was >32-times that in patients while exposure at 4 mcg/kg/day was likely sub-therapeutic.

Juvenile Toxicity: Juvenile toxicity studies were conducted in rats and dogs. There were no findings in these studies that were not identified in studies conducted with adult animals or were considered related to reduced body weight and food consumption.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrADLYXINE®

Lixisenatide injection

Read this carefully before you start taking **ADLYXINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ADLYXINE**.

What is ADLYXINE used for?

ADLYXINE is used along with diet and exercise to improve control of blood sugar levels in adults with type 2 diabetes. It is used in combination with the following medicines when these medicines no longer provide enough control of blood sugar levels on their own:

- metformin
- a sulfonylurea (alone or with metformin)
- pioglitazone (alone or with metformin)
- a basal insulin (alone or with metformin)

How does ADLYXINE work?

- ADLYXINE belongs to a class of medicines called glucagon-like peptide-1 (GLP-1) receptor agonists.
- ADLYXINE helps your body release more insulin when your blood sugar level is high.
- This helps to improve control of your blood sugar levels

What are the ingredients in ADLYXINE?

Medicinal ingredients: lixisenatide

Non-medicinal ingredients: glycerol, hydrochloric acid / sodium hydroxide solution for pH adjustment, metacresol, methionine, sodium acetate trihydrate, water for injection

ADLYXINE comes in the following dosage forms:

solution for injection, 0.05 mg per mL (10 mcg/dose) and 0.1 mg per mL (20 mcg/dose)

Do not use ADLYXINE if you:

- are allergic to lixisenatide or any of the non-medicinal ingredients in ADLYXINE
- have type 1 diabetes
- have diabetic ketoacidosis (a serious complication of diabetes)
- are pregnant, or are planning to become pregnant
- are breastfeeding, or are planning to breastfeed
- are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADLYXINE. Talk about any health conditions or problems you may have, including if you:

- have or have had inflammation of the pancreas known as pancreatitis;
- have stones in your gallbladder (gallstones), high levels of fat in your blood (hypertriglyceridemia) or if you abuse alcohol;
- have severe gastrointestinal disease including a condition called gastroparesis;
- have or have had an inflammatory bowel disease like Crohn disease or ulcerative colitis;
- have had or will have surgery on your stomach or intestines;
- have any heart problems or heart rhythm disturbances such as fast pulse or irregular heart rhythm;
- are taking a sulfonylurea. Taking ADLYXINE with a sulfonylurea can increase your risk of having low blood sugar known as hypoglycemia;
- are taking a basal insulin. Taking ADLYXINE with insulin can increase your risk of having low blood sugar known as hypoglycemia;
- are taking a rapid-acting or short-acting insulin. ADLYXINE has not been studied with this type of insulin.
- have or have had a type of thyroid cancer called medullary thyroid carcinoma or if a family member of yours has had this;
- have or have had an inherited disorder of your endocrine glands called multiple endocrine neoplasia syndrome type 2 or if a family member of yours has had this;
- have severe kidney problems or end-stage renal disease (ESRD) or if you are on dialysis;
- are 65 years of age or older;
- are allergic to other medicines in the GLP-1 receptor agonist class.

Other warnings you should know about:

- Do not inject ADLYXINE into a vein or muscle. It should only be injected under the skin.
- Do not share ADLYXINE with anyone else. You may give another person an infection or get an infection from them.
- ADLYXINE may change how your kidneys function. Your healthcare professional will do blood tests to monitor how well your kidneys are working before you take ADLYXINE and while you are taking ADLYXINE.
- ADLYXINE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.
- **Seek medical attention right away and stop taking ADLYXINE** if you experience severe pain in your stomach area (abdomen) that will not go away with or without vomiting. This could be a sign of inflamed pancreas (acute pancreatitis).
- Gallbladder inflammation or gallstones have been seen in people who took medicines belonging to the same family of anti-diabetic medicines as ADLYXINE. If you have stomach pain, fever, nausea, vomiting, or yellowing of the skin and eyes, **seek medical attention right away and stop taking ADLYXINE.**
- **Driving and using machine:** Taking ADLYXINE with a sulfonylurea or insulin can increase your risk of having low blood sugar known as hypoglycemia. When using ADLYXINE with a sulfonylurea or an insulin, take precautions to avoid hypoglycemia while driving and using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ADLYXINE:

- medicines from the sulfonylurea class used to control blood sugar levels such as glyburide, gliclazide and glimepiride
- a basal insulin used to control blood sugar levels such as insulin glargine and NPH insulin
- medicines that increase your heart rate or that affect your heart rhythm
- warfarin, a blood thinner
- birth control pills
- acetaminophen, used to treat pain and fever
- atorvastatin, used to lower cholesterol
- antibiotics, used to treat bacterial infections
- other medicines taken by mouth.

ADLYXINE slows stomach emptying. It can interact with medicines that need to pass through your stomach quickly like:

- Birth control pills: Take these at least 1 hour before your ADLYXINE injection or at least 11 hours after your ADLYXINE injection.
- Antibiotics: Take these at least 1 hour before your ADLYXINE injection.
- Acetaminophen: Take this at least 1 hour before your ADLYXINE injection.
- Atorvastatin: Take this at least 1 hour before your ADLYXINE injection.
- Ask your healthcare professional when you should take any other medicines that you take by mouth.

Taking other medicines used to treat diabetes like those from the sulfonylurea class or basal insulins in combination with ADLYXINE may cause your blood sugar to get too low (hypoglycemia). Ask your healthcare professional how often you should check your blood sugar. Your healthcare professional may also decide to adjust the dose of your sulfonylurea or basal insulin.

How to take ADLYXINE:

- Read the Pen Instructions for Use included in the package for complete instructions on how to use the ADLYXINE pen and how to inject ADLYXINE.
- Talk to your healthcare professional about how to properly use ADLYXINE before you use it for the first time.
- Use ADLYXINE exactly as it has been prescribed to you by your healthcare professional.
- Pen needles are not included. Ask your healthcare professional which needles to use.
- You must activate your ADLYXINE pen before you use it for the first time. Only activate your pen once.
- ADLYXINE is given as an injection under the skin (subcutaneous injection). You should give yourself the injection in your upper leg (thigh), stomach area (abdomen) or upper arm. You must change the injection site every day. If you are injecting the same area (thigh, abdomen or upper arm), you must change the injection spot in that area every day.
- Do not inject ADLYXINE into a vein or muscle.
- Do not share ADLYXINE with anyone else, even if the needle is changed. You may give another person an infection or get an infection from them.

- Do not use ADLYXINE if it is discolored, contains particles, is cloudy or if there are any signs of leakage. Look through the pen window. The liquid inside the pen should be clear and colourless.

Usual dose:

The recommended starting dose is 10 mcg once a day for 14 days. Your dose will be increased to 20 mcg once a day on day 15. Your healthcare professional may lower your dose temporarily if you do not tolerate 20 mcg once a day.

Take ADLYXINE once a day within the hour before any meal. Choose the meal that suits you best and take ADLYXINE before that same meal every day.

Overdose:

If you think you, or a person you are caring for,have taken too much ADLYXINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of ADLYXINE, take it within the hour before your next meal.
- Never take two doses on the same day to make up for a missed dose.
- Do not stop using ADLYXINE without talking to your healthcare professional. If you stop using it, your blood sugar levels can increase.

What are possible side effects from using ADLYXINE?

These are not all the possible side effects you may have when taking ADLYXINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, vomiting
- diarrhea
- bloating, gas
- constipation
- decreased appetite
- dry mouth
- abdominal pain
- upset stomach, heartburn
- dry mouth
- excessive sweating
- bruising, itching, redness or pain of the injection area
- weakness, tiredness
- headache, dizziness
- motion sickness
- tremor
- nervousness

- cough
- runny or stuffy nose, sneezing
- flu (fever, tiredness, body aches)
- back pain
- muscle pain
- urinary tract infection
- heartbeat that feels too fast, strong or irregular
- blurry vision
- hair loss
- rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Hypoglycemia (low blood sugar):** change in mood, change in vision, confusion, dizziness, fast heartbeat, feeling faint, headache, hunger, shaking, sweating, weakness.			✓
UNCOMMON **Pancreatitis (inflammation of the pancreas):** prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back.			✓
Gallbladder inflammation or gallstones: stomach pain, fever, nausea, vomiting, and yellowing of the skin and eyes			✓
Dehydration from prolonged nausea, vomiting or diarrhea, or from not taking enough liquids by mouth:-light-headedness and fainting particularly upon standing.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Kidney problems including kidney failure: any change in the amount, frequency or colour (pale or dark) of urine.			✓
Severe allergic reactions including anaphylaxis and angioedema: difficulty breathing or swallowing, itching, hives, fainting, sudden swelling of the face, lips, tongue or throat, rash, very fast heartbeat.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Before first use: Store pen in a refrigerator in original package to protect from light, between 2°C to 8°C. Do not freeze.

After first use: Store pen between 2°C to 30°C for up to 14 days. Do not store with needle attached. Replace pen cap after each use to protect from light.

Discard pen 14 days after first use or if heated or frozen.

Keep out of reach and sight of children.

If you want more information about ADLYXINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling sanofi-aventis, at 1-888-852-6887.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised JUL 11, 2023

INSTRUCTIONS FOR USE: ADLYXINE® – 10 MCG PEN

Pen Instructions for Use

Pr Adlyxine®

10 mcg / dose

Lixisenatide injection

50 mcg / mL (3 mL / pen)

SANOFI

ADLYXINE pen is a prefilled pen for the injection of lixisenatide. Your healthcare professional has decided that **ADLYXINE** is appropriate for you, based on your ability to handle **ADLYXINE**. Talk with your healthcare professional about proper injection technique before using **ADLYXINE**.

One pre-filled pen contains 14 doses, each dose contains **10 micrograms (mcg) in 0.2 mL**.

Section 1 – Important Information

Read these instructions carefully before using your ADLYXINE pen.

If you are not able to use ADLYXINE or to follow all the instructions completely on your own, you must use ADLYXINE only if you have help from a person who is able to follow the instructions completely.

Keep this leaflet for future reference.

If you have any questions about ADLYXINE, ask your healthcare professional or call sanofi-aventis at **1-888-852-6887**. See also the Patient Medication Information.

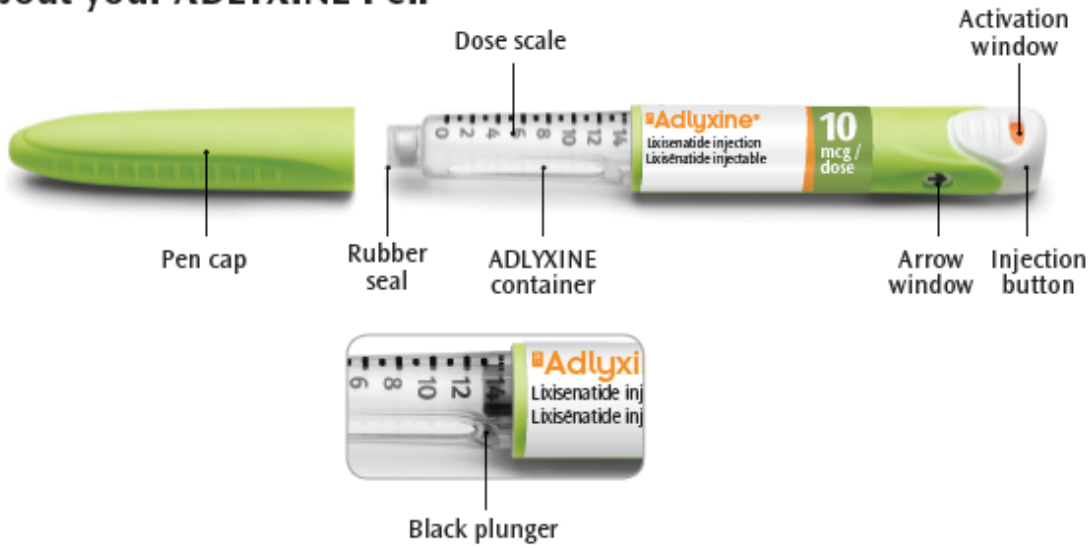
Do not share your ADLYXINE pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

ADLYXINE pen Information

ADLYXINE comes as a pre-filled pen for injection.

- **Only inject one dose per day.**
- Each ADLYXINE pen contains 14 pre-set doses. There is no need to measure each dose.
- Talk with your healthcare professional about how 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.

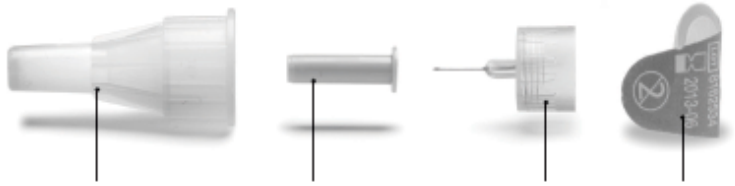
About your ADLYXINE Pen



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

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

About your needles (supplied separately)



- Always use a new needle for each injection. This helps prevent contamination of ADLYXINE or possible needle blockage.
- Only use needles that have been approved for use with ADLYXINE. Ask your healthcare professional which needle gauge and length is best for you.
- Take care not to stick anyone accidentally with the needle. This could possibly pass on infection.

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,** you must activate the new pen. This is a one-time process called 'activation'. Steps 1 to 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 obtain 14 doses from your ADLYXINE pen.

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

New pen
(orange window)

The pen must be activated before injecting your first dose.

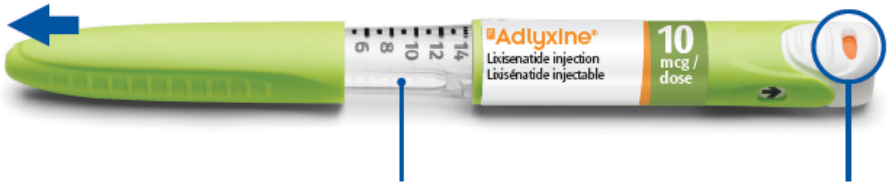
Pen ready for injection
(white window)

The pen is activated and ready for injections.

How to activate your new ADLYXINE pen

Step 1

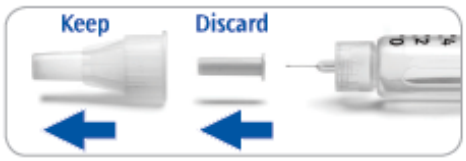
Pull off the pen cap and check the pen



- Check the liquid by looking through the container window. It should be clear, colorless with no particles. If not, do not use this pen. Contact your healthcare professional.
- 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. Keep it straight as you **screw** it on.
- **Pull off** (do not unscrew) the outer and inner needle caps. Keep the outer needle cap it to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

Step 3

Pull injection button out

- **Pull the injection button out firmly until it stops.**

- The arrow will now be pointing towards the needle.

Step 4

Firmly press and hold injection button to discard the liquid

- Point the needle into a suitable 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.
- If no liquid comes out see the Questions and answers section.
- **Check that the activation window is completely white.**

Step 5

The pen is now activated

Do not activate this pen again.

- **For your first injection go directly to** **Section 3 - Step C.**
- You do not need to replace the needle between activation and your first injection if you inject yourself immediately after activation.

Section 3 – Daily use of pen

Only follow this section when the activation window is white.

Inject only one dose each day.

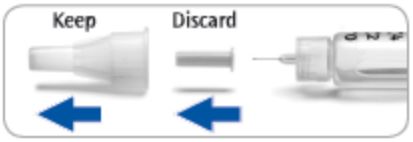
Step A

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. In case of air bubbles see the Questions and answers section.
- 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 B

Screw needle on and remove needle caps



- Always use a **new needle** for each injection.
- Remove protective seal from the outer needle cap.
- Line up the needle with the pen. Keep it straight as you **screw** it on.
- **Pull off** (do not unscrew) the outer and inner needle caps. Keep the outer needle cap to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

Step
C

Pull the injection button out

- **Pull the injection button out firmly until it stops.**

- The arrow will now be pointing towards the needle.

Step
D

Press and hold the injection button to inject the dose

- 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".

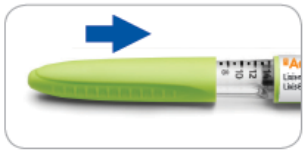
- **Keep the injection button pressed in, hold the pen in place and slowly count to 2** before you pull the needle out of the skin.
- **If you do not hold the injection button in or remove the injector too early you may not get the full dose.**
- Your dose has now been given. Pull the needle out of your skin.

Step
E

Remove and discard 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 professional).

Step
F

Repeat all steps in Section 3 for each injection.

Discard 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 discard
1	___/___/___	___/___/___
2	___/___/___	___/___/___

Storage

General information

- Keep your ADLYXINE pens in a safe place out of the reach and sight of children.
- Protect your ADLYXINE pens from dust and dirt.
- Replace the pen cap after each use in order to protect from light.
- Do not use ADLYXINE 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 ADLYXINE pens in the refrigerator, 2°C to 8°C .
- Do not freeze ADLYXINE pens and do not use ADLYXINE if it has been frozen.
- Allow your pen to warm at room temperature before using.

After activation of the pen:

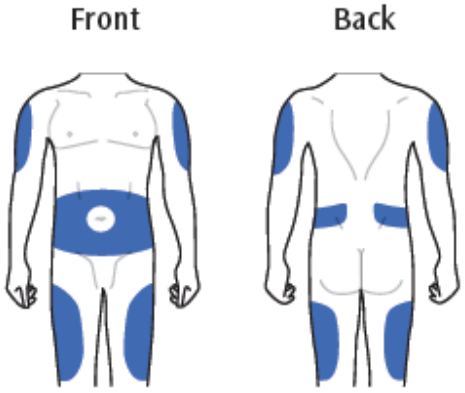
- Once activated, store your ADLYXINE pen between 2°C and 30°C.
- Do not store your ADLYXINE pen with the needle attached. An attached needle might lead to contamination and possible intake of air which might impact the dose accuracy.
- Once your ADLYXINE pen is activated it can be used for up to 14 days. Discard a used ADLYXINE pen after 14 days. Do this even if there is some medicine left in the pen.

Disposal

- Replace the pen cap before disposing of your ADLYXINE pen.
- Put the used ADLYXINE pen in a sharps container right away after use. Do not dispose of the ADLYXINE pen in your household trash.
- If you do not have a sharps 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 labelled to warn of hazardous waste inside the container.

Such containers should be sealed and disposed of properly.

Injection sites



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

Maintenance

- Handle your ADLYXINE pen with care.
- You can clean the outside of your ADLYXINE pen by wiping it with a damp cloth.
- Do not soak, wash or lubricate your ADLYXINE pen - this may damage it.
- If you think your ADLYXINE pen may be damaged, do not use it. Do not try to repair the pen.

Questions and answers

What do I do if I forget to activate the ADLYXINE 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 professional 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 - they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your healthcare professional if you need help.

What do I do if no liquid comes out during activation?
The needle may be blocked or not properly screwed on. Remove the needle from the pen, attach a new one and repeat Steps 4 and 5 of section 2 only. If still no liquid comes out, your ADLYXINE pen may be damaged. Do not use this ADLYXINE pen. Contact your healthcare professional 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 from your skin and remove the needle from the pen. Attach a new needle and repeat Steps D and E of section 3 only. If still no liquid comes out, your ADLYXINE pen may be damaged. Do not use this ADLYXINE pen. Contact your healthcare professional for help.

If you have any questions about ADLYXINE or about diabetes, ask your healthcare professional or call sanofi-aventis Canada Inc. at **1-888-852-6887**.

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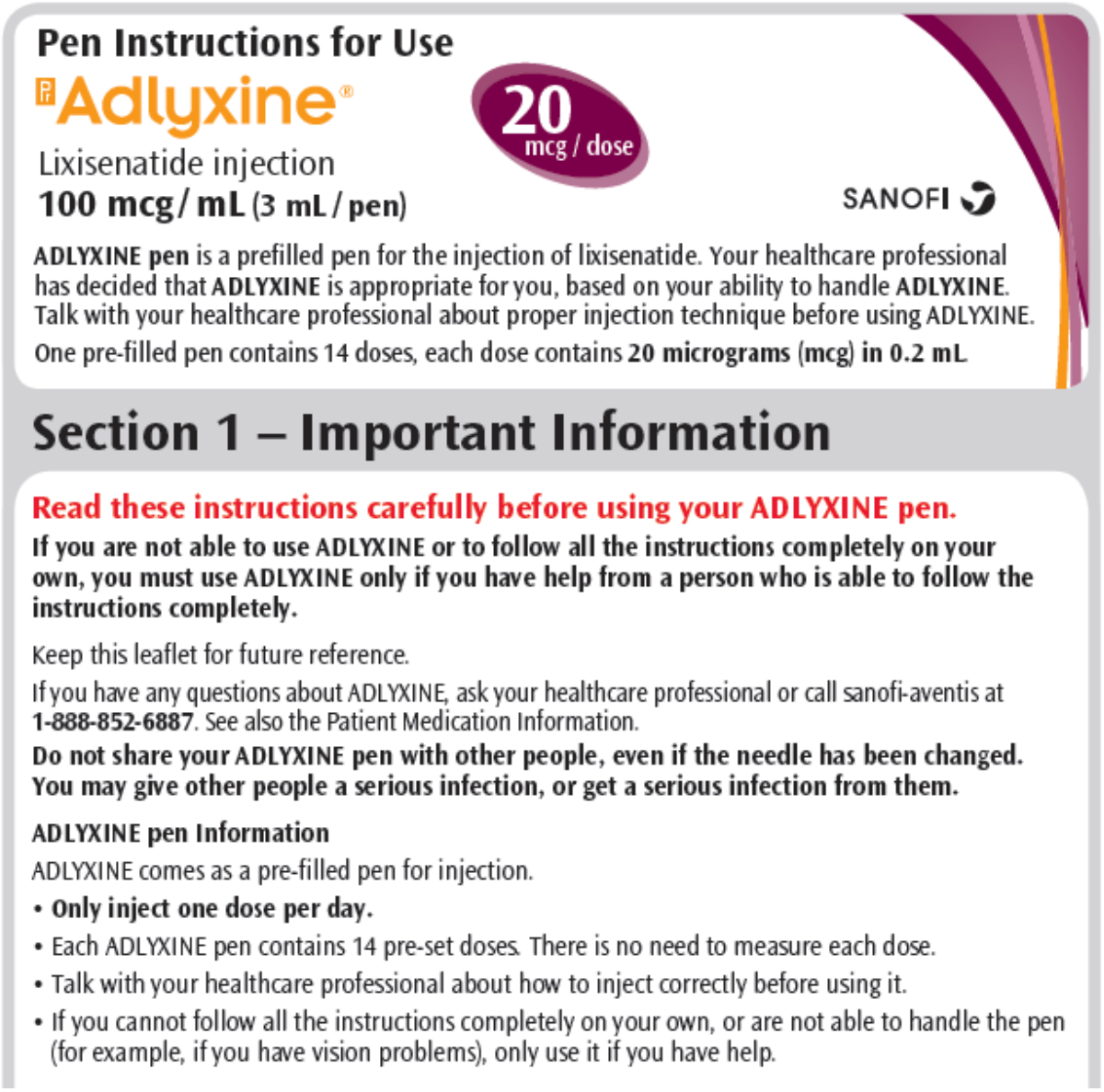
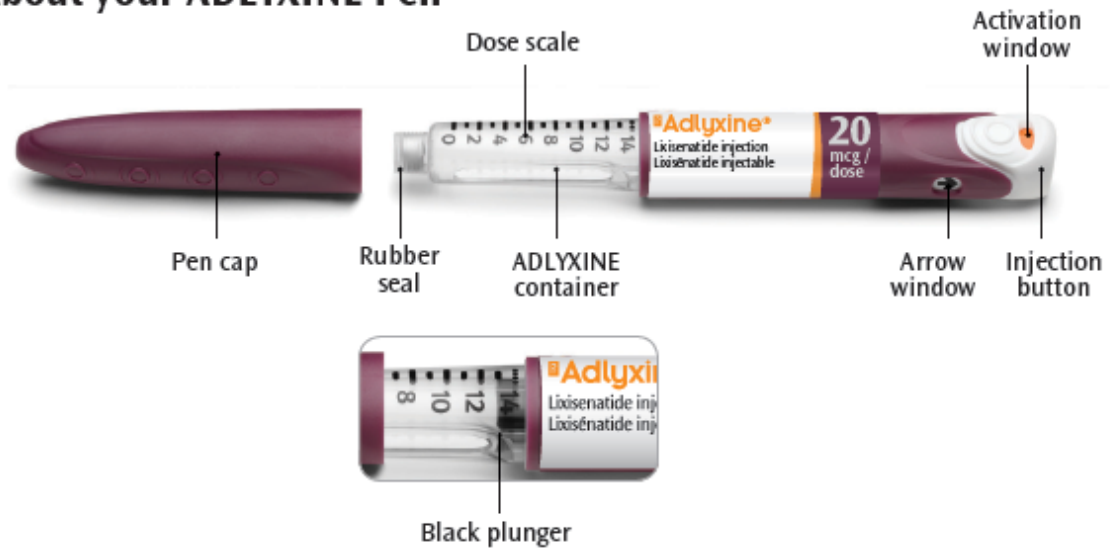
INSTRUCTIONS FOR USE: ADLYXINE® – 20 mcg Pen



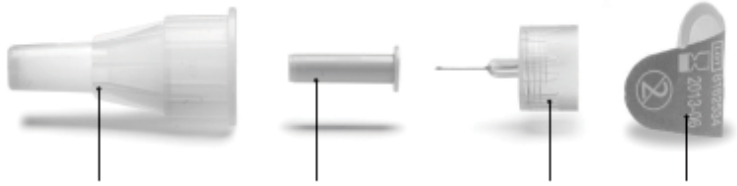
About your ADLYXINE Pen



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

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

About your needles (supplied separately)



- Always use a new needle for each injection. This helps prevent contamination of ADLYXINE or possible needle blockage.
- Only use needles that have been approved for use with ADLYXINE. Ask your healthcare professional which needle gauge and length is best for you.
- Take care not to stick anyone accidentally with the needle. This could possibly pass on infection.

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,** you must activate the new pen. This is a one-time process called 'activation'. Steps 1 to 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 obtain 14 doses from your ADLYXINE pen.

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

New pen
(orange window)

The pen must be activated before injecting your first dose.

Pen ready for injection
(white window)

The pen is activated and ready for injections.

How to activate your new ADLYXINE pen

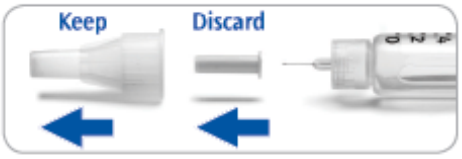
Step 1

Pull off the pen cap and check the pen

- Check the liquid by looking through the container window. It should be clear, colorless with no particles. If not, do not use this pen. Contact your healthcare professional.
- 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. Keep it straight as you **screw** it on.
- **Pull off** (do not unscrew) the outer and inner needle caps. Keep the outer needle cap it to remove the needle later.
- Take care not to injure yourself when the needle is exposed.

Step 3

Pull injection button out

- **Pull the injection button out firmly until it stops.**

- The arrow will now be pointing towards the needle.

Step 4

Firmly press and hold injection button to discard the liquid

- Point the needle into a suitable 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.
- If no liquid comes out see the Questions and answers section.
- **Check that the activation window is completely white**

Step 5

The pen is now activated

Do not activate this pen again.

- **For your first injection go directly to Section 3 - Step C.**
- You do not need to replace the needle between activation and your first injection if you inject yourself immediately after activation.

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Step
C

Pull the injection button out

- **Pull the injection button out firmly until it stops.**

- The arrow will now be pointing towards the needle.

Step
D

Press and hold the injection button to inject the dose

- 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** before you pull the needle out of the skin.
- **If you do not hold the injection button in or 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
E

Remove and discard 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 professional).

Step
F

Repeat all steps in Section 3 for each injection.

Discard 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 discard
1	___/___/___	___/___/___
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Storage

General information

- Keep your ADLYXINE pens in a safe place out of the reach and sight of children.
- Protect your ADLYXINE pens from dust and dirt.
- Replace the pen cap after each use in order to protect from light.
- Do not use ADLYXINE 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 ADLYXINE pens in the refrigerator, 2°C to 8°C.
- Do not freeze ADLYXINE pens and do not use ADLYXINE if it has been frozen.
- Allow your pen to warm at room temperature before using.

After activation of the pen:

- Once activated, store your ADLYXINE pen between 2°C and 30°C.
- Do not store your ADLYXINE pen with the needle attached. An attached needle might lead to contamination and possible intake of air which might impact the dose accuracy.
- Once your ADLYXINE pen is activated it can be used for up to 14 days. Discard a used ADLYXINE pen after 14 days. Do this even if there is some medicine left in the pen.

Disposal

- Replace the pen cap before disposing of your ADLYXINE pen.
- Put the used ADLYXINE pen in a sharps container right away after use. Do not dispose of the ADLYXINE pen in your household trash.
- If you do not have a sharps container, you may use a household container that is:
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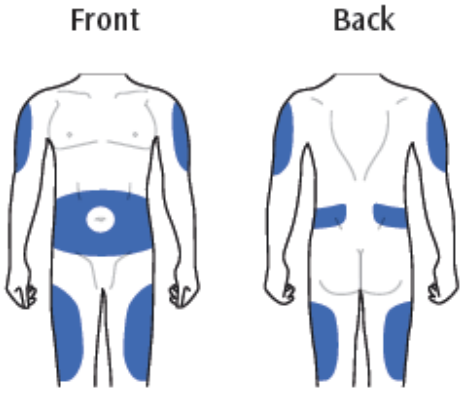

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Maintenance

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