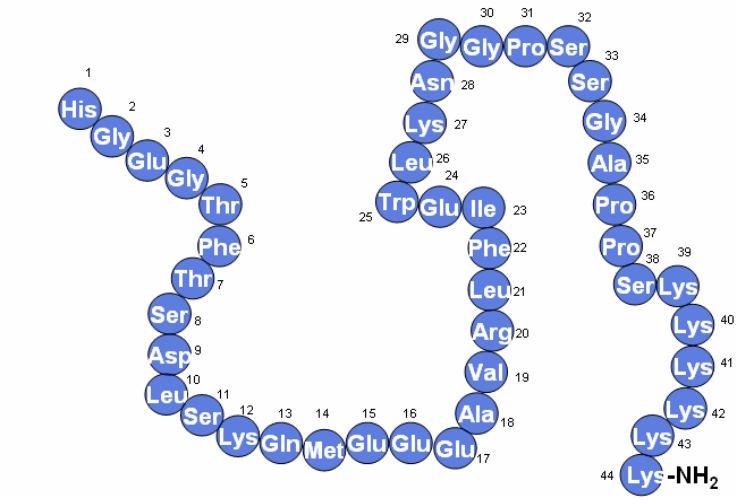
***For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory***

***This package insert is continually updated: Please read carefully before using a new pack.***

**Lixisenatide Prefilled Solution for Injection**
**10µg and 20µg**

**LYXUMIA™**

LYXUMIA™ (lixisenatide), is a peptide containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44). It is an amorphous, hygroscopic, white to off-white powder. The order of the amino acids is given in the figure below. Its molecular weight is 4858.5, and the empirical formula is C215H347N61O65S with the following chemical structure:




**PHARMACEUTICAL FORM**

LYXUMIA™ is available as a sterile solution for injection in prefilled pen in two dosage strengths : 0.05mg/mL and 0.1 mg/mL. The product will be administered parenterally (subcutaneously).

**COMPOSITION**

Active ingredient: lixisenatide 10 mcg, and 20 mcg

A) Each dose (0.2 ml) contains
Lixisenatide.....10 micrograms
metacresoL.....0.27 % w/v (as preservative)
Excipients.....q.s.
(3 mL cartridge in a green pre-filled pen, 0.05 mg/ml)

B) Each dose (0.2 ml) contains
Lixisenatide.....20 micrograms
metacresoL.....0.27 % w/v (as preservative)
Excipients.....q.s.
(3 mL cartridge in a burgundy pre-filled pen, 0.1 mg/ml)

**Disposable pen (3mL)**

3 mL glass cartridge assembled in a 14-dose prefilled pen

**Excipients**: Glycerol 85%, Sodium acetate trihydrate, methionine, metacresol, hydrochloric acid/sodium hydroxide solution for pH adjustment, water for injections.

## INDICATIONS

LYXUMIA™ is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients who are not controlled on existing therapy:

In combination with the following oral antidiabetics
- metformin,
- a sulphonylurea, or
- a combination of these agents,

In combination with a basal insulin:
- alone,
- in combination with metformin, or
- in combination with a sulphonylurea.

## DOSAGE AND ADMINISTRATION

***General***

The starting dose is 10 mcg (µg) LYXUMIA™ once daily for 14 days.
Then, the LYXUMIA™ dose should be increased to 20 mcg once daily, which is the maintenance dose.

When LYXUMIA™ is added to existing metformin therapy, the current metformin dose can be continued unchanged.

When LYXUMIA™ is added to existing therapy of a sulphonylurea or a combination of a sulphonylurea and a basal insulin, a reduction in the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia (see Precautions).

The use of LYXUMIA™ does not require specific blood glucose monitoring. However, when used in combination with a sulphonylurea or a basal insulin, blood glucose monitoring or blood glucose self-monitoring may become necessary to adjust the doses of the sulphonylurea or the basal insulin.

***Special Populations***

***Children***

The safety and effectiveness of LYXUMIA™ in pediatric patients below the age of 18 years have not yet been established.

***Elderly***

No dose adjustment is required based on age.

***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. There is no therapeutic experience in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease and therefore, it is not recommended to use LYXUMIA™ in these populations.

***Administration***

LYXUMIA™ is administered once daily within the hour prior to any meal of the day. It is preferable that LYXUMIA™ is injected before the same meal every day, when the most convenient meal has been chosen.
If a dose of LYXUMIA™ is missed, it should be injected within the hour prior to the next meal. LYXUMIA™ is to be injected subcutaneously in the thigh, abdomen or upper arm. LYXUMIA™ should not be administered intravenously or intramuscularly.

## CONTRAINDICATIONS:

LYXUMIA™ is contraindicated in patients with known hypersensitivity to lixisenatide or to any of the inactive ingredients in the formulation

## WARNINGS

***Use In Type 1 Diabetes***

There is no therapeutic experience with LYXUMIA™ in patients with type 1 diabetes mellitus and it should not be used in these patients. LYXUMIA™ should not be used for treatment of diabetic ketoacidosis.

***Risk of pancreatitis***

Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, LYXUMIA™ should be discontinued ; if acute pancreatitis is confirmed, LYXUMIA™ should not be restarted. Use with caution in patients with a history of pancreatitis.

## PRECAUTIONS

***Use in patients with severe gastroparesis***

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. LYXUMIA™ has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis and therefore, the use of LYXUMIA™ is not recommended in these patients.

***Risk of hypoglycaemia***

Patients receiving LYXUMIA™ with a sulphonylurea or with a combination of a basal insulin and a sulphonylurea may have an increased risk of hypoglycaemia. Reduction of the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia.

## INTERACTIONS

Lixisenatide is a peptide and is not metabolised by cytochrome P450. In in vitro studies, lixisenatide did not affect the activity of cytochrome P450 isozymes or human transporters tested.

The delay of gastric emptying with lixisenatide may influence absorption of orally administered medicinal products. For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, patients should be advised to take those medicinal products at least 1 hour before or 11 hours after lixisenatide injection.

**Acetaminophen (Paracetamol)**

Following administration of a single dose of paracetamol 1000 mg, paracetamol AUC and t 1/2 were unchanged whatever the timing of its administration (before or after the lixisenatide injection). When administered 1 or 4 hours after the lixisenatide injection, $C_{max}$ of paracetamol was decreased by 29 % and 31 % respectively and median $t_{max}$ was delayed by 4.5 and 2 hours respectively. Based on these results, no dose adjustment for paracetamol is required.

**Oral contraceptives**

Following administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg /levonorgestrel 0.15 mg) 1 hour before or 11 hours after subcutaneous injection of lixisenatide, $C_{max}$, AUC, t1/2 and $t_{max}$ of ethinylestradiol and levonorgestrel were unchanged. The administration of

ethinylestradiol and levonorgestrel 1 hour or 4 hours after the subcutaneous lixisenatide injection did not affect AUC and t1/2 whereas $C_{max}$ of ethinylestradiol was decreased by 52 % and 39% respectively and $C_{max}$ of levonorgestrel was decreased by 46 %and 20% respectively and median $t_{max}$ was delayed by 2 to 4 hours.
The reduction in $C_{max}$ is of limited clinical relevance and no dose adjustment for oral contraceptives is required.

**Atorvastatin**
When lixisenatide and atorvastatin 40 mg were co- administered in the morning, the exposure of atorvastatin was not affected, $C_{max}$ was slightly decreased and $t_{max}$ was increased from 1.5 hour to 4 hours.
No such increase for $t_{max}$ was observed when atorvastatin is administered in the evening and lixisenatide in the morning but the AUC and $C_{max}$ were increased by 27 % and 66 % respectively.

These changes are not clinically relevant and therefore, no dose adjustment for atorvastatin is required when coadministered with lixisenatide.

**Warfarin**
After concomitant administration of warfarin 25 mg with lixisenatide, there was no effects on $C_{max}$, AUC or INR (International Normalised Ratio) while $t_{max}$ was delayed by 7 hours.
Based on these results, no dose adjustment for warfarin is required when coadministered with lixisenatide.

**Digoxin**
After concomitant administration of lixisenatide and digoxin 0.25 mg, the AUC of digoxin was not affected. The $t_{max}$ was delayed by 1.5 hour and $C_{max}$ was reduced by 26%.
Based on these results, no dose adjustment for digoxin is required when coadministered with lixisenatide.

**Ramipril**
After concomitant administration of lixisenatide and ramipril 5 mg during 7 days, the AUC of ramipril was slightly decreased by 21 % while the $C_{max}$ was decreased by 63 %.The AUC and $C_{max}$ of the active metabolite (ramiprilat) were not affected. $T_{max}$ of ramipril and ramiprilat was delayed by approximately 2.5 hours.
Based on these results, no dose adjustment for ramipril is required when coadministered with lixisenatide.

**PREGNANCY**
There are no adequate data from the use of LYXUMIA™ in pregnant women. Studies in animals have shown reproductive toxicity (see section teratogenicity). The potential risk for humans is unknown. LYXUMIA™should not be used during pregnancy and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with LYXUMIA™ should be discontinued.

**LACTATION**
It is unknown if LYXUMIA™ is excreted in human milk. Because of lack of experience, LYXUMIA™ should not be used during breastfeeding.

**DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS**
No studies on the effects on the ability to drive and use machines have been performed. When used in combination with a sulphonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

**ADVERSE REACTIONS**
*The following CIOMS frequency rating is used, when applicable:*
*Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and < 1 %;*
*Rare ≥0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).*

Over 2600 patients have received LYXUMIA™ either alone or in combination with metformin, a sulphonylurea (with or without metformin) or a basal insulin (with or without metformin, or with or without a sulphonylurea) in 8 large placebo- or active-controlled phase III studies.

The most frequently reported adverse reactions during clinical trials were **nausea** and **vomitin**g. These reactions were **mostly mild and transient**.

Table 1 lists adverse reactions reported from placebo- and active-controlled phase III studies over the entire treatment period. The table presents adverse reactions by preferred term that occurred with an incidence $>$ 5% if the frequency was higher among LYXUMIA™ treated patients than patients treated with all comparators. The table also includes adverse reactions with a frequency $\geq$ 2% in the LYXUMIA™ group if the frequency was $>$ 2 times the frequency for the comparator group.

Table 1 : Adverse reactions reported during placebo- and active-controlled phase III studies during the entire treatment period (including the period beyond the main 24-week treatment period in studies of ≥76 weeks of total treatment).

| **MedDRA system organ classes / adverse reaction terms** | **Frequency of occurrence** | |
|---|---|---|
| Reactions | Very common | Common |
| **Infections and infestations** | | |
| **Influenza** | | X |
| **Upper respiratory tract infections** | | X |
| **Metabolism and nutrition disorders** | | |
| **Symptomatic hypoglycaemia** (when treatment includes a sulphonylurea and / or a basal insulin) | X | |
| **Nervous system disorders** | | |
| **Headache** | X | |
| **Dizziness** | | X |
| **Gastrointestinal disorders** | | |
| **Nausea** | X | |
| **Diarrhoea** | X | |
| **Vomiting** | X | |
| **Dyspepsia** | | X |
| **Musculoskeletal and connective tissue disorders** | | |
| **Back pain** | | X |

***Hypoglycaemia***

In patients taking Lyxumia in monotherapy or in combination with metformin alone, symptomatic hypoglycemia was common and the rate was similar in Lyxumia patients and placebo patients during the entire treatment period.

In patients taking Lyxumia in combination with a sulphonylurea or a basal insulin, symptomatic hypoglycemia was very common.

During the entire treatment period, the rate was not substantially higher in Lyxumia patients than in placebo patients when Lyxumia was given in combination with :

- a sulphonylurea and metformin,
- a basal insulin alone,
- a basal insulin and metformin.

During the entire treatment period, when Lyxumia was given with a sulphonylurea alone, symptomatic hypoglycaemia occurred in 22.7% of Lyxumia treated patients versus 15.2% with placebo. When

Lyxumia was given with a sulphonylurea and a basal insulin, symptomatic hypoglycaemia occurred in 47.2% of Lyxumia treated patients compared to 21.6% with placebo.Overall, the incidence of severe symptomatic hypoglycaemia was uncommon (0.4% in Lyxumia patients and 0.2% in placebo patients) during the entire treatment period of the Phase III placebo-controlled studies.

***Gastrointestinal disorders***
Nausea and vomiting are the most frequently reported adverse reactions during the main 24-week treatment period. The incidence of nausea was higher in the Lyxumia group (26.1 %) compared to the placebo group (6.2 %) and the incidence of vomiting was higher in the Lyxumia (10.5 %) than in the placebo group (1.8 %). They were mostly mild and transient and occured during the first 3 weeks after starting treatment. Thereafter, they progressively decreased during the following weeks.

The incidence of nausea was lower in the Lyxumia group (24.5 %) compared to the exenatide twice daily group (35.1%) and was similar for the other gastrointestinal events.

***Injection site reactions***
**Injections site reactions** have been reported in 3.9 % of the patients receiving Lyxumia while they were reported in 1.4 % of patients receiving placebo during the main 24-week treatment period. The majority of reactions were mild in intensity and usually did not result in discontinuation of the treatment.

***Immunogenicity***
**Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-lixisenatide antibodies following treatment with Lyxumia** and, at the end of the main (24-week) treatment period in placebo-controlled studies, 69.4 % of lixisenatide patients had a positive antibody status. However **the change in $HbA_{1c}$ from baseline was similar regardless of the antibody status (positive or negative).**
Of lixisenatide-treated patients, 79.3 % had either a negative antibody status or an antibody concentration below the lower limit of quantification. The other 20.7 % of patients had a quantified antibody concentration and some of these patients had diminished efficacy associated with high anti-lixisenatide antibody concentration.
**There were no difference in the overall safety profile in patients regardless of the antibody status with the exception of an increase of the incidence of injection site reactions for antibody positive patients**. The majority of injection site reactions were mild, regardless of antibody status.

There was no cross-reactivity versus either native glucagon or endogenous GLP-1.

***Allergic reactions***
**Allergic reactions (such as anaphylactic reaction, angioedema and urticaria) have been reported** in 0.4 % of Lyxumia patients compared to less than 0.1% in placebo patients during the main 24-week treatment period.

***Withdrawal***
The incidence of treatment discontinuation due to adverse events was 7.4% for Lyxumia compared to 3.2% in the placebo group during the main 24-week treatment period. The most common adverse events which led to treatment discontinuation in the Lyxumia group were nausea (3.1%) and vomiting (1.2%).

**OVERDOSE**

***Signs and symptoms***

During clinical studies, doses up to 30 µg of lixisenatide twice a day were administered to type 2 diabetic patients in a 13-week study. They were well tolerated and only an increased incidence of gastrointestinal disorders was observed.

***Management***
In case of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and the LYXUMIA™ dose should be reduced to the prescribed dose.

## PHARMACODYNAMICS

### *Mode of Action/Pharmacodynamic characteristics*

#### *Mechanism of Action*

Lixisenatide is a potent and 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 the pancreatic beta cells.

Lixisenatide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in intracellular cyclic adenosine monophosphate (cAMP). Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved. Lixisenatide further showed a trend towards insulinotropic activity, including enhancement of insulin biosynthesis and stimulation of beta-cell proliferation in animals.

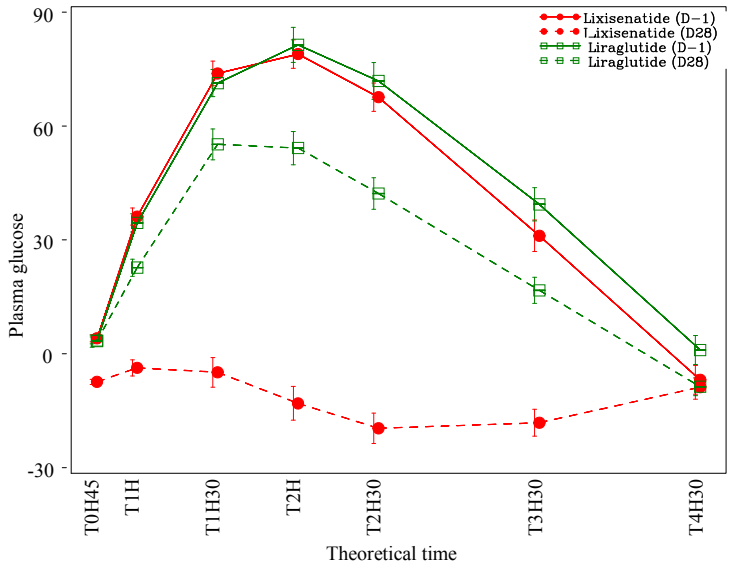
Lixisenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation. The effect on gastric emptying might also contribute to body weight reduction.

#### *Pharmacodynamic Properties*

When administered once daily, lixisenatide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

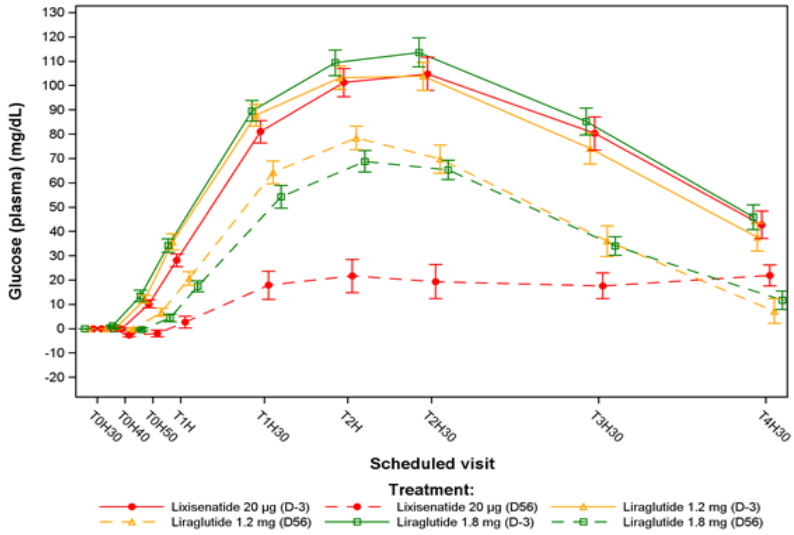
This effect on post-prandial glucose was confirmed in a 4-week study versus liraglutide 1.8 mg once a day in combination with metformin. Lixisenatide 20 µg once a day demonstrated superior reduction compared to liraglutide in area under the curve of post-prandial plasma glucose after a test-meal. ( Standardized solid breakfast (See figure 1)

Figure 1: Mean (± SEM) pre-meal value substratedpost-prandial plasma glucose profile on Day -1(baseline) and Day 28, by treatment




This was also confirmed in an 8-week study versus liraglutide, administered before breakfast, in combination with insulin glargine with or without metformin. In this study the reduction from baseline in the AUC0:30-4:30h of plasma glucose after a test-meal (standardised solid breakfast) was: -13.33 h*mmol/L (-240.15 h*mg/dL) in the lixisenatide group, -7.32 h*mmol/L (-131.82 h*mg/dL) in the liraglutide 1.2 mg group and -8.72 h*mmol/L (- 157 h*mg/dL) in the liraglutide 1.8 mg group. See Figure 2.

Figure 2: Mean (± SEM) pre-meal value substrated post-prandial plasma glucose profiles (mg/dL) on Day - 3 (baseline) and Day 56 – by treatment.




***Clinical efficacy/Clinical Studies***

The effects of LYXUMIA™ on glycaemic control were mainly evaluated in six randomised double-blind, placebo-controlled clinical studies and one randomised, open-label, active-controlled study versus exenatide.
These studies included 3825 patients with type 2 diabetes (2445 patients randomised to lixisenatide), 48.2 % men and 51.8% women.
768 subjects (447 randomised to lixisenatide) were ≥65 years of age and 103 subjects (57 randomised to lixisenatide) were ≥75 years of age.
In the completed Phase III studies, it was observed that more than 90% of the patient population was able to remain on the once daily maintenance dose of 20 µg LYXUMIA™ at the end of the 24-week treatment period.

- Glycaemic control

LYXUMIA™ demonstrated superior effect compared to placebo in reducing glycosylated haemoglobin (HbA1c) regardless of the background treatment and LYXUMIA™ once daily showed a non inferior HbA1c reduction compared to exenatide twice daily. This effect on HbA1c was sustained in long term studies for up to 2 years.
The HbA1c reduction was significant with either a once daily morning or evening administration.

Add-on combination therapy with oral antidiabetics
LYXUMIA™ in combination with metformin, a sulphonylurea or a combination of these agents showed clinically and statistically significant reductions in HbA1c, in fasting plasma glucose and in 2-hour post-prandial glucose after a test-meal compared to placebo at the end of the main 24-week treatment period. (Tables 2 and 3).

<u>Add-on treatment to metformin alone</u>

Table 2: Placebo-controlled studies in combination with metformin (24-week results).

| | Metformin as background therapy | | | | |
|---|---|---|---|---|---|
| | Lixisenatide 20 µg | | Placebo (N= 159) | Lixisenatide 20 µg | Placebo (N= 170) |
| | Two-step dose initiation * (N= 160) | One-step dose initiation * (N= 160) | | Morning (N= 255) | Evening (N= 255) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mean HbA1c (%) | | | | | | |
| Baseline | 8.12 | 7.99 | 8.03 | 8.07 | 8.07 | 8.02 |
| LS mean change from baseline | -0.83 | -0.92 | -0.42 | -0.87 | -0.75 | -0.38 |
| Patients (%) achieving HbA1c < 7.0% | 42.1 | 47.4 | 24.1 | 43.0 | 40.6 | 22.0 |
| Mean body weight (kg) | | | | | | |
| Baseline | 88.08 | 90.30 | 87.86 | 90.14 | 89.01 | 90.40 |
| LS mean change from baseline | -2.68 | -2.63 | -1.63 | -2.01 | -2.02 | -1.64 |

*Two dose initiation regimens of 2-week duration were evaluated in this study; they both were followed by a maintenance period with LYXUMIA™ 20 µg once daily. The one-step initiation (10 µg for two weeks) followed by 20 µg for maintenance is the regimen recommended for use.

In an active-controlled study, LYXUMIA™ once daily showed a non inferior HbA1c reduction compared to exenatide twice daily at the end of the main 24-week treatment period (respectively - 0.79 % and - 0.96%) and a similar percentage of patients achieved an HbA1c less than 7% in the LYXUMIA™ group (48.5 %) and in the exenatide group (49.8 %).

In an open label study in type 2 Diabetes Mellitus diagnosed at least for one year, inadequately controlled with metformin alone, patients were randomized to either inject lixisenatide 0-60 minutes before breakfast or 0-60 minutes before the patient's main meal (this could either be breakfast, lunch or dinner). Treatment period was 24 weeks. The primary efficacy end-point was HbA1c change from baseline to week 24.

The mean changes from baseline to Week 24 in HbA1c were -0.65% for the main meal group and -0.74% for the breakfast group. The study demonstrates that lixisenatide administered before the main meal is noninferior to lixisenatide administered before breakfast.

Table 3: Lixisenatide Main meal versus Breakfast dosing (24-week results) primary and secondary endpoints

| Lixisenatide Main meal (N= 224) | Lixisenatide Breakfast (N= 226) |
|---|---|
| Mean HbA1c (%) | |
| Baseline 7.85 | 7.93 |
| LS mean change from baseline -0.65 | -0.74 |
| Patients (%) achieving HbA1c < 7.0% 43.6 | 42.8 |
| Average 7 point Self-Monitoring Plasma Glucose (SMPG; mmol/L) | |
| Mean Baseline 9.38 | 9.68 |
| LS mean change from Baseline -0.80 | -1.10 |
| Mean body weight (kg) | |
| Baseline 95.40 | 92.75 |
| LS mean change from baseline -2.60 | -2.80 |

Safety between the two groups was similar to what was has been seen in other clinical trials (see section "Adverse reactions").
The number of symptomatic hypoglycaemia events was low; incidence of symptomatic hypoglycaemia was 5.8% for lixisenatide given before a main meal compared to 2.2% when given before breakfast

Add-on treatment to a sulphonylurea alone or in combination with metformin

Table 4: Placebo –controlled study in combination with a sulphonylurea (24-week results)

| | Sulphonylurea as background therapy with or without metformin | |
|---|---|---|
| | Lixisenatide 20 µg (N= 570) | Placebo (N= 286) |
| Mean HbA1c (%) | | |
| Baseline | 8.28 | 8.22 |
| LS mean change from baseline | -0.85 | -0.10 |
| Patients (%) achieving HbA1c < 7.0 % | 36.4 | 13.5 |
| Mean body weight (kg) | | |
| Baseline | 82.58 | 84.52 |
| LS mean change from baseline | -1.76 | -0.93 |

Add-on combination therapy with a basal insulin

LYXUMIA™ given with a basal insulin alone, or with a combination of a basal insulin and metformin, or a combination of a basal insulin and a sulphonylurea resulted in statistically significant reductions in HbA1c and in 2-hour post-prandial glucose after a test- meal compared to placebo. At the end of the main 24-week treatment period, the reduction in insulin daily dose from baseline was greater in the LYXUMIA™ group than in the placebo group.

Table 5 Placebo –controlled study in combination with a basal insulin (24-week results)

| | Basal insulin as background therapy Alone or in combination with metformin | | Basal insulin as background therapy Alone or in combination with a sulphonylurea | |
|---|---|---|---|---|
| | Lixisenatide 20 µg (N= 327) | Placebo (N= 166) | Lixisenatide 20 µg (N= 154) | Placebo (N= 157) |
| Mean HbA1c (%) | | | | |
| Baseline | 8.39 | 8.38 | 8.53 | 8.53 |
| LS mean change from baseline | -0.74 | -0.38 | -0.77 | 0.11 |
| Patients (%) achieving HbA1c < 7.0% | 28.3 | 12.0 | 35.6 | 5.2 |
| Mean change in basal insulin dose (U) | | | | |
| Baseline | 53.62 | 57.65 | 24.87 | 24.11 |
| LS mean change from baseline | -5.62 | -1.93 | -1.39 | -0.11 |
| Mean body weight (kg) | | | | |
| Baseline | 87.39 | 89.11 | 65.99 | 65.60 |
| LS mean change from | -1.80 | -0.52 | -0.38 | 0.06 |

baseline

Patients with type 2 diabetes with basal insulin combined with 1-3 oral anti-diabetic agents were enrolled in an open-label randomized study for insulin intensification. After 12-week of optimal insulin glargine titration with or without metformin, inadequately controlled patients were randomized to add single dose of lixisenatide or a single dose (QD) of insulin glulisine (both before the largest meal) or insulin glulisine administered three times a day (TID) for 26 weeks.

Lixisenatide was non-inferior to both insulin glulisine regimens on HbA1c reduction based on noninferiority margin of 0.4%. Lixisenatide was superior on body weight versus insulin glulisine TID.

As opposed to both insulin glulisine treatment regimens, Lixisenatide reduced body weight.
The rate of symptomatic hypoglycaemic events was lower with lixisenatide compared to insulin glulisine QD and TID (36% and 51%, respectively).

Table 6: Active-controlled study in combination with basal insulin with or without metformin (26-week results) - (mITT) and safety population

| | Lixisenatide | Insulin glulisine QD | Insulin glulisine TID |
|---|---|---|---|
| Mean HbA1c % | N = 297 | N = 298 | N = 295 |
| LS Change from baseline | -0.63 | -0.58 | -0.84 |
| LS Mean difference (SE) of lixisenatide vs | | -0.05 (0.059) | 0.21 (0.059) |
| 95% CI | | (-0.170 to 0.064) | (0.095 to 0.328) |
| Mean Body Weight | N = 297 | N = 298 | N = 295 |
| LS Change from baseline | -0.63 | +1.03 | +1.37 |
| LS Mean difference (SE) of lixisenatide vs | | -1.66 (0.305) | -1.99 (0.305) |
| 95% CI | | (-2.257 to -1.062) | (-2.593 to -1.396)* |
| Symptomatic hypoglycemia | N = 298 | N = 301 | N = 294 |
| Rate ratio lixisenatide vs | | 0.64 | 0.49 |
| 95% CI | | (0.45 to 0.89) | (0.36 to 0.69) |

*p<0.0001

- Fasting plasma glucose

The mean decrease in fasting plasma glucose obtained with LYXUMIA™ treatment ranged from 0.42 mmol/L to 1.19 mmol/L at the end of the main 24-week treatment period in placebo-controlled studies.

- Post-prandial glucose

Treatment with LYXUMIA™ resulted in reductions in 2-hour post-prandial glucose after a test-meal statistically superior to placebo whatever the background treatment.
These reductions ranged from 4.51 to 7.96 mmol/L from baseline at the end of the main 24-week treatment period across all studies in which post-prandial glucose was measured; 26.2% to 46.8% of patients had a 2-hour post-prandial glucose value below 7.8 mmol/L.

- Body weight

Treatment of LYXUMIA™ in combination with metformin, basal insulin and/or a sulphonylurea resulted in a body weight mean reduction up to 2.96 kg at the end of the main 24-week treatment period which was sustained in long term studies up to 2 years.

The body weight reduction is independent from the occurrence of nausea and vomiting.

- Beta cell function

In clinical studies, LYXUMIA™ improved the beta-cell function as measured by the homeostasis model assessment for beta-cell function (HOMA-β).
Restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose was demonstrated in patients with type 2 diabetes (n=20) after a single dose of LYXUMIA™.

- Heart rate

No increase in heart rate was seen in all controlled phase III studies.
In a 4-week study versus liraglutide, mean heart rate decreased by 3.6 bpm in the lixisenatide group (20 µg once a day) while it increased by 5.3 bpm in the liraglutide (1.8 mg once a day) group.

- Blood pressure

Systolic and diastolic blood pressure reductions up to 2.1mmHg and up to 1.5 mmHg respectively were observed in phase III placebo-controlled studies.

**People aged ≥70 years**
Lixisenatide as add-on therapy in people aged ≥ 70 years with type 2 diabetes The efficacy and safety of lixisenatide, administered before breakfast, in people aged ≥70 years with type 2 diabetes 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 (randomization ratio 1:1). Overall, 37% of the patients were ≥75 years old (N=131) and 31% had moderate renal impairment (N=107). Patients received stable dose(s) of oral antidiabetic drug(s) (OAD) and/or basal insulin as background therapy. Sulfonylureas or glinides were not used with basal insulin as background therapy.

Lixisenatide provided significant improvements in HbA1c (-0.64% change compared to placebo; 95% CI: -0.810% to -0.464%; p<0.0001), from a mean baseline HbA1c of 8.0%, largely due to a significant improvement in postprandial plasma glucose (PPG) (-5.05 mmol/L change compared to placebo; 95% CI: -5.960 mmol/L to -4.132 mmol/L; p<0.0001).

The rate of patients with decrease >0.5% in HbA1c without experiencing documented symptomatic hypoglycemia was approximately three times higher in the lixisenatide group (58% in lixisenatide versus 22% in placebo; 95% CI: 26.71% to 44.97%).

Decrease in body weight (-1.32 kg change versus placebo; 95% CI: -1.862 kg to -0.769 kg; p<0.0001) was observed with no impact on nutritional status, as assessed by Mini Nutritional Assessment-Short Form (MNA-SF) score (-0.17 change versus placebo; 95% CI: -0.422 to 0.088).

**Cardiovascular Outcomes Study**
The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome. The primary composite efficacy endpoint was the time to the first occurrence of 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. CV secondary endpoints included a composite of the primary endpoint,or hospitalization for heart failure or coronary revascularization. Changes in urinary albumin excretion at 108 weeks were also a pre-specified secondary endpoint.

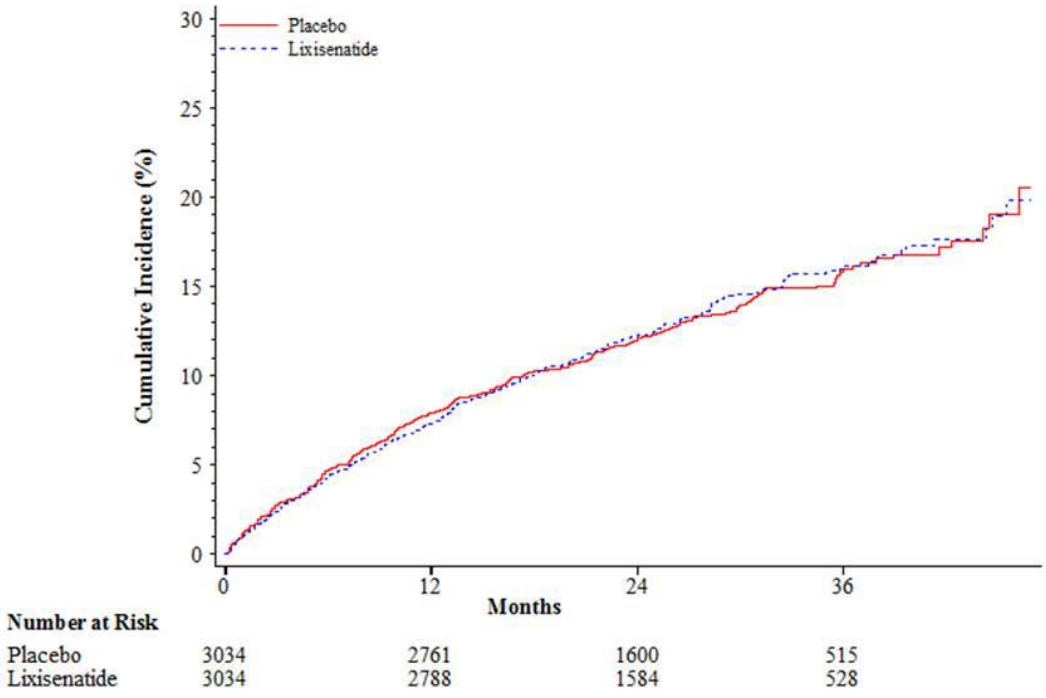
Overall, 6068 patients were randomized 1:1 to either placebo or lixisenatide 20 mcg (following a starting dose of 10 mcg during the first 2 weeks) and were included in the efficacy analyses. The demographics and baseline characteristics were well balanced between treatments. The median age at study entry was 60 years. Approximately 69% of the patients were males and 75% were Caucasian. The majority of

patients were either obese or overweight with a median BMI of 29.4 kg/m2. The mean duration of diabetes was 9.3 years. More than 75% of patients had impaired renal function and more than 20% had an estimated GFR less than 60 mL/min/ 1.73 m2. Use of CV medications at baseline was similar between treatments; overall platelet aggregation inhibitors (aspirin and/or clopidogrel) were used by 97.5% of patients, statins by 92.7%, ACE inhibitors and/or angiotensin II antagonists by 86.8%, and beta-blockers by 84.4%. Prior to study entry, 93.9% of patients used at least 1 glucose-lowering medication, including metformin (69.9%),sulfonylureas (37.3%) and insulin (47.6%). During the study, antidiabetic medications were adjusted by the investigators per standard of care, hence similar glycemic control was expected in the two treatment groups.

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. Mean HbA1c (±SD) in the lixisenatide and placebo groups was 7.72 (±1.32)% and 7.64 (±1.28)% at baseline and 7.46 (±1.51)% and 7.61 (±1.48)% at 24 months, respectively.

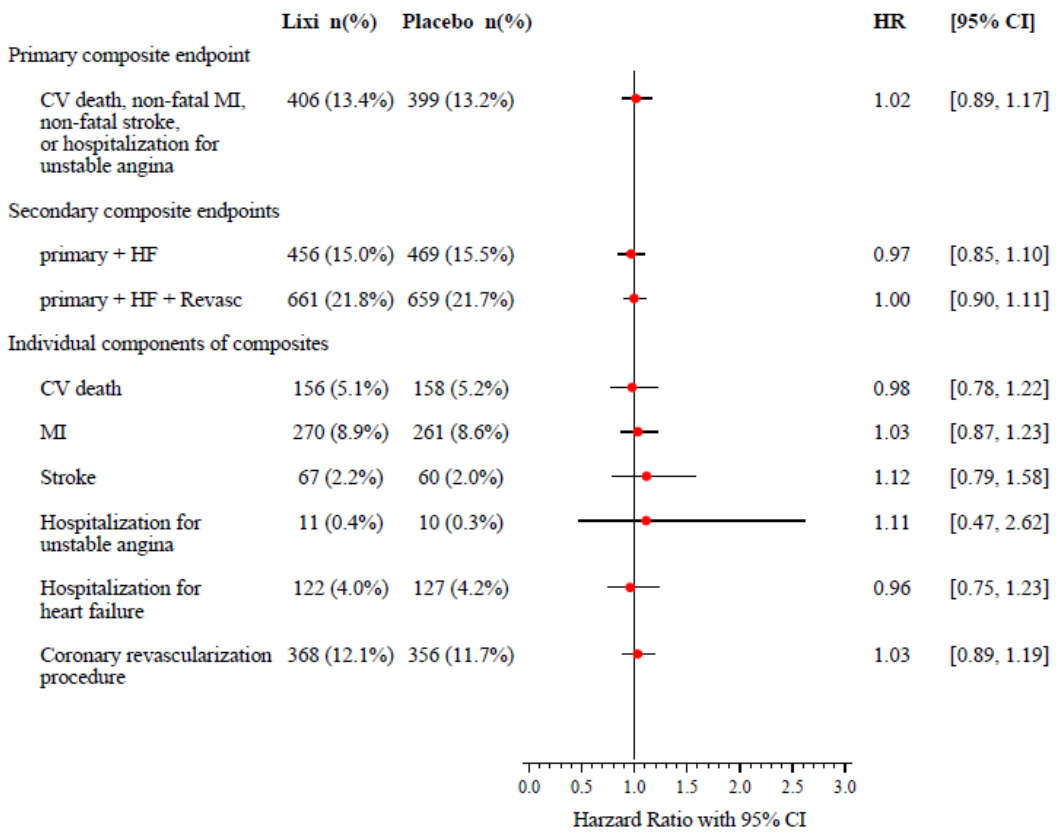
The results of the primary composite efficacy endpoint are shown in Figure 4. The hazard ratio (HR) for lixisenatide versus placebo was 1.017, with an associated 2-sided 95% confidence interval (CI) of 0.886 to 1.168.

**Figure 4. Kaplan-Meier cumulative curves of the primary CV endpoint (time to the first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina) - ITT population**




Similar percentages between treatments were observed for the primary and secondary endpoints, and for all the individual components of the composite endpoints (Figure 5).

**Figure 5: Forest plot: analyses of each individual cardiovascular event -- ITT population**




CV: cardiovascular, MI: myocardial infarction, HF: hospitalization for heart failure, Revasc: coronary revascularization procedure, HR: hazard ratio, CI: confidence interval.

Only positively adjudicated events by the Cardiovascular events Adjudication Committee are included.

| | **Placebo (N=3034) n (%)** | **Lixisenatide (N=3034) n (%)** | **Hazard ratio** | **95% CI** |
|---|---|---|---|---|
| **Primary Composite Endpoint** CV death, non-fatal MI, non- fatal stroke, hospitalization for UA | 399 (13.2) | 406 (13.4) | 1.02 | 0.89, 1.17 |
| **Secondary Composite endpoints** | | | | |
| Primary+ HF | 469 (15.5) | 456 (15.0) | 0.97 | 0.85, 1.10 |
| Primary + HF + revascularization | 659 (21.7) | 661 (21.8) | 1.00 | 0.90, 1.11 |
| **Individual** | | | | |

| **components of composites** | | | | |
|---|---|---|---|---|
| CV Death | 158 (5.2) | 156 (5.1) | 0.98 | 0.78, 1.22 |
| Myocardial infarction | 261 (8.6) | 270 (8.9) | 1.03 | 0.87, 1.23 |
| Stroke | 60 (2.0) | 67 (2.2) | 1.12 | 0.79, 1.58 |
| Hospitalization for Unstable Angina | 10 (0.3) | 11 (0.4) | 1.11 | 0.47, 2.62 |
| Hospitalization for Heart Failure | 127 (4.2) | 122 (4.0) | 0.96 | 0.75, 1.23 |
| Coronary revascularization | 356 (11.7) | 368 (12.1) | 1.03 | 0.89, 1.19 |

Urinary albumin excretion increased from baseline to Week 108 in both groups, consistent with progression of the underlying disease, but a smaller increase was observed in lixisenatide compared to placebo. The percent change from baseline (expressed as geometric mean UACR) was + 24.17 ± 2.84% in lixisenatide versus + 34.21 ± 3.09% in placebo.

## PHARMACOKINETICS

***Absorption***

Following subcutaneous administration to patients with type 2 diabetes, the rate of lixisenatide absorption is rapid and not influenced by the dose administered. Irrespective of the dose and whether lixisenatide was administered as single or multiple doses, the median tmax is 1 to 3.5 hours in patients with type 2 diabetes. There are no clinically relevant differences in the rate of absorption when lixisenatide is administered subcutaneously in the abdomen, thigh, or arm.

***Distribution***

Lixisenatide has a moderate level of binding (55%) to human proteins.

The volume of distribution after subcutaneous administration of lixisenatide in patients with type 2 diabetes ranged between 90 and 140 L after single administration and between 90 and 120 L at steady state irrespective of the dose administered.

***Metabolism***

As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism.

***Elimination***

After multiple dose administration in patients with type 2 diabetes, mean apparent elimination half-life generally ranged from 1.5 to 4.5 hours and the mean apparent clearance ranged from 20 to 67 L/h at steady state.

***Special populations***

*Gender*

Gender does not affect the pharmacokinetics of lixisenatide based on a population pharmacokinetic data analysis.

*Elderly*

Age has no clinically relevant effect on the pharmacokinetics of lixisenatide based on a population pharmacokinetic data analysis in patients with type 2 diabetes and a pharmacokinetic study conducted in elderly non diabetic subjects.

*Race*

Ethnic origin had no clinically relevant effect on the pharmacokinetics of lixisenatide based on the results of pharmacokinetic studies in Caucasian, Japanese and Chinese subjects and based on a population pharmacokinetic data analysis which included Caucasian and Asian (Japanese) patients.

*Hepatic impairment*
As lixisenatide is cleared primarily by the kidney, no pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.

*Renal impairment*
There were no relevant differences in mean clearance, Cmax and AUC of lixisenatide between subjects with normal renal function and subjects with mild or moderate impaired renal function. Mean Cmax and AUC increased with further increases in the degree of renal impairment.

**NON-CLINICAL SAFETY DATA**
**CARCINOGENICITY**
In 2-year subcutaneous carcinogenicity studies, no C-cell carcinoma was observed at any dose level in mice and the no effect level (NOEL) for C-cell carcinomas was 40 µg/kg twice daily in rats. Proliferative thyroid C-cell effects were seen in rats and mice at very high exposure ratios (respectively ≥913-fold and ≥272-fold) when compared to human exposure at the therapeutic dose. These findings are considered to be caused by a GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive.

**GENOTOXICITY**
Lixisenatide had no genotoxic effects, based on one in vivo micronucleus test in mice and in vitro tests: the modified Ames test with or without metabolic activation, and in vitro mammalian chromosome aberration test in cultured human lymphocytes

**TERATOGENICITY**
Fetal growth retardation, skeletal findings and delayed ossification occurred in rats at maternally toxic doses resulting in exposures ≥4.6-fold the mean exposure at the MRHD. In rabbits, increased incidences of sternebrae and rib variations were observed at maternally toxic doses at exposures ≥345-fold the mean exposure at the MRHD.In the pre-postnatal toxicity study in rats lixisenatide caused slightly increased pup mortality at 200 µg/kg BID, and decreased growth in male pups, slightly decreased suckling and minor developmental delay in fur growth at 20 and 200 µg/kg BID. No functional or behavioural toxicity was observed in offspring of rats administered lixisenatide at any dose.

**IMPAIRMENT OF FERTILITY**
Lixisenatide had no effects on male and female fertility in rats.

**INCOMPATIBILITIES / COMPATIBILITIES**
In the absence of compatibility study, lixisenatide cannot be mixed with other medicinal products.

**STORAGE CONDITIONS AND SHELF-LIFE**

Before first use, LYXUMIA™ must be stored refrigerated between +2°C and +8°C in the outer packaging in order to protect from light.

After first use, LYXUMIA™ can be kept at a temperature not exceeding 30°C and not in a refrigerator. 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. Do not use if frozen. The pen must be discarded 14 days after first opening.

Shelf life: Refer outer carton

**PREPARATION AND HANDLING**

Inspect LYXUMIA™ before each use. LYXUMIA™ must only be used if the solution is clear, colourless, with no particles visible.

**Manufactured by:**
M/s Sanofi-Aventis Deutschland GmbH, Industriepark Hochst, 65926 Frankfurt am Main, Germany.

**Importer: Sanofi-Synthelabo (India) Private Ltd.,**
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Updated: October 2015
Reference: Lixisenatide CCDS V 5.0 dated September 2015