DATA SHEET

1 LYXUMIA INJECTION, SOLUTION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LYXUMIA 10µg solution for injection (green injection pen)

Each dose (0.2 mL) contains 10 µg of lixisenatide (0.05 mg/ ml).

LYXUMIA 20µg solution for injection (purple injection pen)

Each dose (0.2 mL) contains 20 µg of lixisenatide (0.1 mg/mL).

LYXUMIA TREATMENT INITIATION PACK (1 green + 1 purple injection pen)

Each dose (0.2 mL) from the 10 µg pen contains 10 µg of lixisenatide (0.05 mg/mL). Each dose (0.2 mL) from the 20 µg pen contains 20 µg of lixisenatide (0.1 mg/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lixisenatide is an amorphous, hygroscopic, white to off-white powder.

Lyxumia solution is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lyxumia is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with metformin, metformin and sulphonylurea, basal insulin and metformin, basal insulin and sulphonylurea when these, together with diet and exercise, do not provide adequate glycaemic control (see sections CLINICAL TRIALS and PRECAUTIONS (Risk of Hypoglycemia)) for available data on the different combinations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose
The starting dose is 10 mcg (µg) Lyxumia once daily for 14 days.

Then, the Lyxumia dose should be increased to 20 mcg (µg) once daily, which is the maintenance dose.

If a dose of Lyxumia is missed, it should be injected within the hour prior to the next meal.

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

When Lyxumia is added to a combination of a basal insulin and a sulphonylurea, a reduction in the dose of the basal insulin or the sulphonylurea may be considered according to individual response to reduce the risk of hypoglycaemia (see section 4.4).

When used in combination with basal insulin and a sulphonylurea, blood glucose monitoring may become necessary to adjust the doses of the basal insulin or the sulphonylurea.

USE IN THE ELDERLY (≥ 65 years)
No dosage adjustment is required based on age. The clinical experience in patients ≥ 75 years is limited.

CHILDREN
The safety and effectiveness of Lyxumia in paediatric patients below the ages of 18 years have not been established.

HEPATIC IMPAIRMENT
No dose adjustment is needed in patients with hepatic impairment.

RENAL IMPAIRMENT
No dose adjustment is required for patients with mild renal impairment (creatinine clearance: 50-80 mL/min).

Moderate renal impairment
There is limited therapeutic experience in patients with moderate renal impairment (creatinine clearance: 30-<50 ml/min) and Lyxumia should be used with caution in this population.

Severe 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.

Method of administration

Lyxumia is administered once daily within the hour before a meal (either breakfast, lunch or dinner).

It is preferable that the prandial injection of Lyxumia is performed 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.

4.3 CONTRAINDICATION

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

USE IN TYPE 1 DIABETES

There is no therapeutic experience with Lyxumia in patients with type 1 diabetes mellitus and it is not recommended for these patients.

Lyxumia should not be used for treatment of diabetic ketoacidosis

POPULATIONS NOT STUDIED

Lixisenatide has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors. There is limited experience in patients with congestive heart failure.

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.

USE IN PATIENTS WITH SEVERE GASTROINTESTINAL DISEASE

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.

USE IN PATIENTS WITH RENAL IMPAIRMENT

Moderate renal impairment

There is limited therapeutic experience in patients with moderate renal impairment (creatinine clearance: 30-<50 ml/min) and Lyxumia should be used with caution in this population.

Severe 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.

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. When used in combination with a sulphonylurea or a basal insulin, blood glucose monitoring may become necessary to adjust the doses of the sulphonylurea or the basal insulin. (see section 4.8)

PAEDIATRIC USE

The safety and effectiveness of Lyxumia in paediatric patients below the age of 18 years have not yet been established.

USE IN THE ELDERLY

No dose adjustment is required based on age. The clinical experience in patients ≥ 75 years is limited.

A total of 447 subjects aged 65 years or older received lixisenatide in these studies. There were no age-related differences in the change in HbA1c values from baseline to endpoint for subjects treated with lixisenatide.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 at therapeutically relevant concentrations.

The delay of gastric emptying with lixisenatide may influence absorption of orally administered medicines. 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.

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 2 and 1.75 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, $t_{1/2}$ 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 $t_{1/2}$ 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 1 to 3 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, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours.

No such increase for t_{max} was observed when atorvastatin 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 AND OTHER COUMARIN DERIVATIVES

After concomitant administration of warfarin 25 mg with repeated dosing of lixisenatide 20µg, there were no effects on AUC or INR (International Normalised Ratio) while C_{max} was reduced by 19% and t_{max} was delayed by 7 hours.

Based on these results, no dose adjustment for warfarin is required when coadministered with lixisenatide; however frequent monitoring of INR in patients on warfarin and/or coumarin derivatives is recommended at the time of initiation or ending of lixisenatide treatment

DIGOXIN

After concomitant administration of lixisenatide and digoxin 0.25 mg, the AUC of digoxin was not affected. 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 increased 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

FERTILITY

Hypospermatogenesis and focal sperm stasis were observed in dogs treated subcutaneously with lixisenatide. However, this occurred only at high doses (yielding ≥64 times the plasma AUC in patients at the maximum recommended human dose) and dogs were seen to be more sensitive to such toxicity by lixisenatide compared with other species. No related effect on spermatogenesis was seen in healthy men.

PREGNANCY (CATEGORY B3)

There are no adequate data from the use of Lyxumia in pregnant women. Studies in animals have shown reproductive toxicity. 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.

Foetal growth retardation, skeletal abnormalities and delayed ossification occurred in rats treated during gestation to maternally toxic doses resulting in exposures ≥0.5-fold the mean exposure at the maximum recommended human dose (MRHD). In rabbits, impaired ossification and increased incidences of sternebrae abnormalities and rib variations were observed at maternally toxic doses (≥50µg/kg/day subsutaneously) yielding exposures ≥40-fold the mean exposure at the MRHD.

In the pre-/postnatal toxicity study in rats subcutaneous treatment with lixisenatide during gestation and lactation caused slightly increased pup mortality at 200µg/kg BID and decreased growth in male pups, and slightly decreased suckling and minor developmental delay in fur growth at 20 and 200 µg/kg BID (occurring in conjunction with maternal toxicity). No functional or behavioural toxicity was observed in the offspring of rats administered lixisenatide at doses up to 200µg/kg BID.

LACTATION

It is unknown if lixisenatide is excreted in human milk. A study in lactating rats showed very low transfer of lixisenatide and its metabolites into milk. Due to lack of experience, Lyxumia should not be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 UNDESIRABLE EFFECTS

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 vomiting. These reactions were mostly mild and transient.

In addition, hypoglycemia (when Lyxumia was used in combination with sulphonylurea and/or a basal insulin) and headache occurred.

In an active-controlled study in combination with metformin, the incidence of nausea in the lixisenatide group was 24.5% compared to 35.1% in the exenatide twice daily group and the incidence of symptomatic hypoglycaemia with lixisenatide was 2.5% during the 24-week main treatment period compared to 7.9% in the exenatide group.

Allergic reactions have been reported in 0.4% of Lyxumia patients.

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 lixisenatide treated patients than patients treated with all comparators. The table also includes adverse reactions with a frequency ≥1% in the lixisenatide group if the frequency was >2 times the frequency for the comparator group.

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).
Within each system organ class, adverse reactions are presented in order of decreasing frequency.

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).

System Organ Class	Frequency of occurrence		
	Very common	Common	Uncommon
Infections and infestations		Influenza	
		Upper respiratory tract infection	
		Cystitis	
		Viral infection	
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia (in combination with a sulphonylurea and / or a basal insulin)	Hypoglycaemia (in combination with metformin alone)	
Nervous system disorders	Headache	Dizziness	
		Somnolence	
Gastrointestinal disorders	Nausea	Dyspepsia	
	Vomiting		
	Diarrhoea		
Skin and subcutaneous tissue disorders			Urticaria
Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions		Injection site pruritus	

HYPOGLYCAEMIA

In patients taking Lyxumia in monotherapy, symptomatic hypoglycaemia occurred in 1.7% of lixisenatide treated patients and in 1.6% of placebo treated patients. When Lyxumia is used in combination with metformin alone, symptomatic hypoglycaemia occurred in 7.0% of lixisenatide patients and in 4.8% of placebo patients during the entire treatment period.

In patients taking Lyxumia in combination with a sulphonylurea and metformin, symptomatic hypoglycaemia occurred in 22.0% of lixisenatide treated patients and in 18.4% of placebo treated patients during the entire treatment period (3.6% absolute difference). When Lyxumia is used in combination with a basal insulin with or without metformin, symptomatic hypoglycaemia occurred in 42.1% of lixisenatide patients and in 38.9% of placebo patients during the entire treatment period (3.2% absolute difference).

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 (7.5% absolute difference). 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 (25.6% absolute difference).

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 occurred during the first 3 weeks after starting treatment. Thereafter, they progressively decreased during the following weeks.

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. Less than 1% of patients discontinued lixisenatide treatment due to an injection site reaction.

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, 69.8 % of lixisenatide patients had a positive antibody status.

The percentage of patients who were antibody positive was similar at the end of the entire 76-week treatment period. At the end of the main 24-week treatment period, 32.2% of the patients having a positive antibody status had an antibody concentration above the lower limit of quantification, and at the end of the entire 76-week treatment period, 44.7% of the patients had an antibody concentration above the lower limit of quantification. After stopping the treatment, few antibody positive patients were followed-up for antibody status; the percentage decreased to approximately 90% within 3 months and 30% at 6 months or beyond.

The change in HbA1c from baseline was similar regardless of the antibody status (positive or negative).

When the levels of antibodies in the lixisenatide-treated patients were quantified, 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. In the subset of patients (5.2%) with the highest antibody concentrations, the mean improvement in HbA1c at Week 24 and at Week 76 was in a clinically relevant range; however there was variability in the glycaemic response and 1.9% had no decrease in HbA1c.

The antibody status (positive or negative) is not predictive for a diminished HbA1c change in individual patients.

There was 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 (4.7% in antibody positive patients compared to 2.5% in antibody-negative patients during the entire treatment period) 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.

Anaphylactic reactions were reported in 0.2% of the lixisenatide treated patients vs. none in the placebo group. Most of these reported allergic reactions were mild in severity. One case of anaphylactoid reaction was reported during clinical trials with lixisenatide.

HEART RATE

Cardiac arrhythmias particularly tachycardia (0.8% vs <0.1%) and palpitations (1.5% vs 0.8%) have been reported in lixisenatide patients compared to placebo treated patients.

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%).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

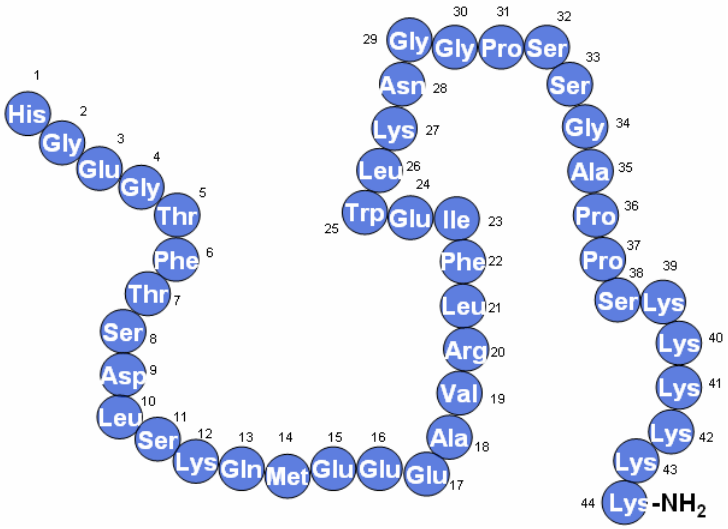
During clinical studies, doses up to 30 µg of lixisenatide twice a day were administered to type 2 diabetic patients in a 13-week study. They were well tolerated and only an increased incidence of gastrointestinal disorders was observed.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or the New Zealand National Poisons Information Centre on 0800 POISON or 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

The structure of lixisenatide is a peptide containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44). The order of the amino acids is given in the figure below. Its molecular weight is 4858.5, and the empirical formula is $C_{215}H_{347}N_{61}O_{65}S$ with the following chemical structure:



Molecular Weight: 4858.5

CAS Registry Number: 320367-13-3

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

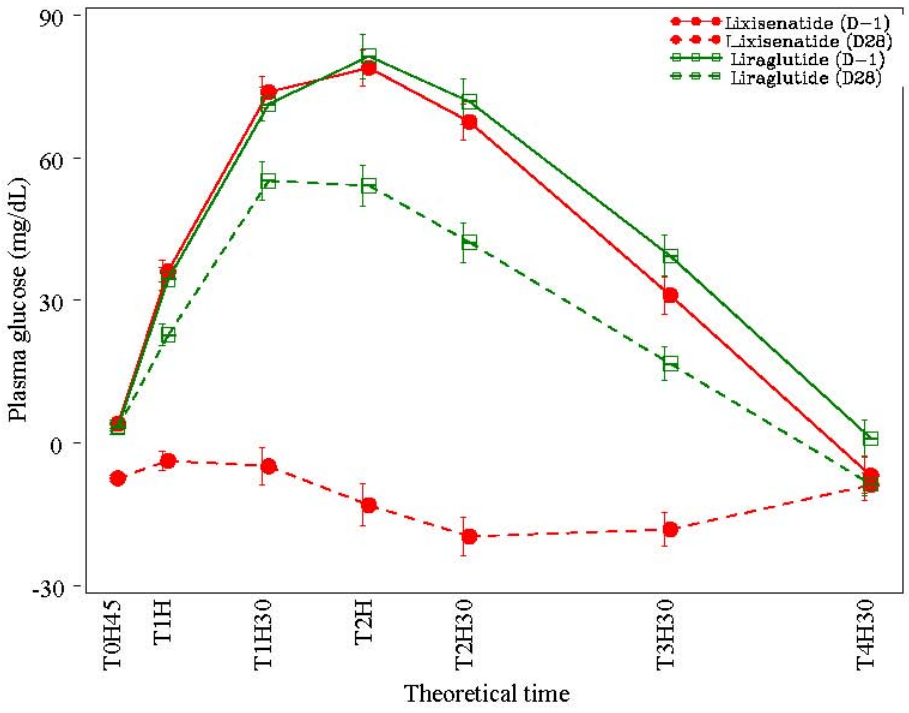
Lixisenatide is a potent and selective GLP-1 receptor agonist (Ki = 1.33nM in radioligand binding experiments). The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.

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. 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.

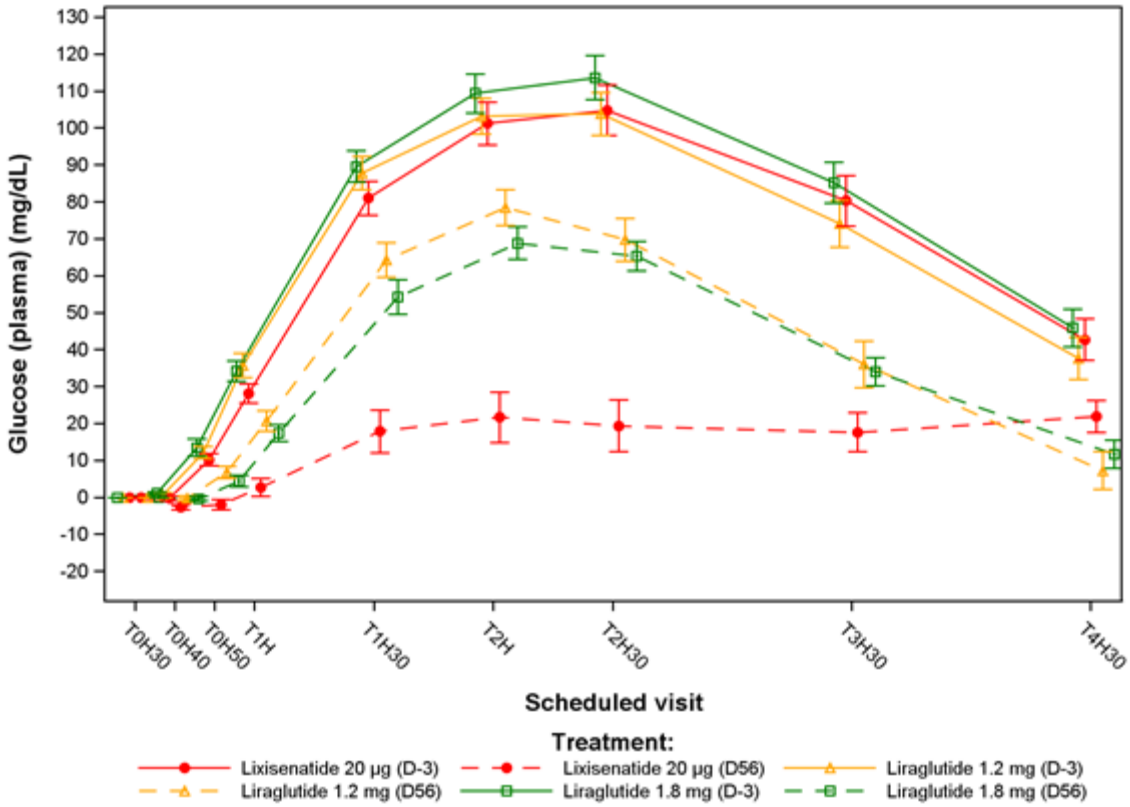
When administered once daily, lixisenatide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes. This effect on post-prandial glucose was confirmed in a 4-week study versus liraglutide 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 (standardised solid breakfast). (see Figure 1)

Figure 1 - Mean (± SEM) concentration of post-prandial plasma glucose change from pre-meal values 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 $AUC_{0:30\text{-}4:30h}$ 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



5.2 PHARMACOKINETIC PROPERTIES

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 t_{max} is 1 to 3.5 hours in patients with type 2 diabetes. There are no clinically relevant differences in the extent of absorption when lixisenatide is administered subcutaneously in the abdomen, thigh, or arm, while the rate of absorption when injecting in the thigh was slightly lower (t_{max} of 2.5 hours instead of 2.0 hours) compared to injecting in the arm or abdomen in a study conducted in healthy volunteers. Following subcutaneous administration of a single 10µg dose of lixisenatide in the abdomen, thigh and arm, mean C_{max} was 56.7 pg/mL, 48.6 pg/mL (ratio thigh versus abdomen: 0.86; CI: 0.79-0.94) and 56.9 pg/mL [ratio arm versus abdomen: 1.00; CI: 0.92-1.09], respectively.

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

The apparent 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
Lixisenatide was found to be extensively metabolized by human kidney and liver S9 fractions in vitro. As a peptide, lixisenatide is presumed to be 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.

Excretion
After multiple dose administration in patients with type 2 diabetes, mean apparent 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
No dosage adjustment is required based on gender. Gender had no clinically meaningful effect on the pharmakinetics of lixisenatide based on the results of population pharmacokinetic data analysis of male and female subjects and pharmacokinetic study in healthy subjects

Paediatric use
The safety and effectiveness of Lyxumia in paediatric patients below the age of 18 years have not yet been established.

Elderly patients
In a pharmacokinetic study in elderly non diabetic subjects, administration of lixisenatide 20 µg resulted in a mean increase of lixisenatide AUC by 29 % in the elderly population (11 subjects between 65 and 74 years and 7 subjects aged ≥75 years) compared to 18 subjects aged 18 to 45 years, likely related to reduced renal function in the older age group.

Age had no clinically relevant effect on the pharmacokinetics of lixisenatide based on a population pharmacokinetic data analysis in patients with type 2 diabetes.

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.

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
A single-dose, open-label study evaluated the pharmacokinetics of lixisenatide 5 micrograms in subjects with varying degrees of renal impairment (classified using the Cockcroft-Gault formula for Creatinine Clearance (CLcr)) compared to healthy subjects. Compared to healthy subjects (N=4; CLcr 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, respectively, (CLcr 60-89, 30-59 and 15-29 mL/min, respectively); plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively.

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY
Lixisenatide had no genotoxic effects, based on one in vivo micronucleus test in mice (involving IV administration up to 5000 µg/kg) and in vitro tests: the modified Ames test with or without metabolic activation, and in vitro mammalian chromosome aberration test in cultured human lymphocytes.

CARCINOGENICITY
Lixisenatide caused thyroid C-cell tumours in 2-year subcutaneous carcinogenicity studies in rodents. In mice, thyroid C-cell adenoma (together with focal C-cell hyperplasia) was increased at ≥400 µg/kg/day, yielding systemic exposure levels ≥29-fold greater than in humans at the maximum recommended human dose. No treatment-related increase in tumour incidence was seen in mice at 80 µg/kg/day (relative exposure, 7). In rats, focal C-cell hyperplasia and C-cell adenoma were increased at all dose levels tested (≥80 µg/kg/day: yielding exposure ratios ≥9), and C-cell carcinoma was observed at ≥400 µg/kg/day (yielding ≥35-times the human exposure). These findings are considered to be caused by a GLP-l receptor-mediated mechanism to which rodents are particularly sensitive. Human relevance cannot presently be completely excluded.

EFFECT ON LABORATORY TESTS
No studies on the effects of Lyxumia on laboratory tests have been performed.

CLINICAL TRIALS

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 at least 76 weeks.

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. (Table 2 and Table 4).

Add-on treatment to Metformin alone

In two separate placebo–controlled studies when lixisenatide was used in combination with metformin, significant improvements in glucose control were observed compared to placebo (see Table 2).

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

	Metformin as background therapy					
	Two step versus one step dose regimen			Morning versus evening dose regimen		
	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

	Metformin as background therapy					
	Two step versus one step dose regimen			Morning versus evening dose regimen		
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 lixisenatide 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 in combination with metformin, lixisenatide 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%, with a mean treatment difference of 0.17% [95% CI: 0.033, 0.297).

Table 3 - Active –controlled study in combination with metformin (24-week results)

	Metformin as background therapy	
	Lixisenatide 20mcg once daily	Exenatide 10 mcg twice daily
	(N= 315)	(N= 315)
Mean HbA1c (%) Baseline	7.97	7.96
LS mean change from baseline	-0.79	-0.96
Patients (%) achieving HbA1c < 7.0%	48.5	49.8%
Mean body weight (kg) Baseline	94.51	96.69
LS mean change from baseline	-2.96	-3.98

In an open label study in type 2 Diabetes Mellitus diagnosed at least for one year, inadequately controlled with metformin alone, patients were randomised 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 non-inferior to lixisenatide administered before breakfast.

Table 4 - Lixisenatide main meal versus breakfast dosing (24-weeks 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
Mean body weight (kg)	95.40	92.75
Baseline		
LS mean change from baseline	-2.60	-2.80

Safety between the two groups was similar to what has been seen in other clinical trials.

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 with metformin and a sulphonylurea

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

	Sulphonylurea ± 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

Lixisenatide given in one study with a basal insulin alone or in combination with metformin, or given in another study with a basal insulin alone or in combination with a sulphonylurea (see INDICATION) 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 insulin daily dose was significantly reduced in the lixisenatide group as compared to the placebo group in the two separate studies conducted and reported in Table 6

Table 6 - Placebo –controlled studies in combination with 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	Placebo	Lixisenatide 20 µg	Placebo
	(N= 327)	(N= 166)	(N= 154)	(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 baseline	-1.80	-0.52	-0.38	0.06

*Performed in Asian population

Patients with type 2 diabetes with basal insulin combined with at least one oral anti-diabetic agent were enrolled in an open-label randomised study for insulin intensification. After 12 weeks of optimal insulin glargine titration with or without metformin, inadequately controlled patients were randomised 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. The co-primary endpoints were based on HbA1c change from baseline to Week 26 and body weight change from baseline to Week 26 (lixisenatide versus insulin glulisine TID).

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 three times a day 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 administered as a single dose (QD) and three times a day (TID) (36% and 51%, respectively).

Table 7 - Active-controlled study in combination with basal insulin with or without metformin (Week 26 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)*

*p<0.0001

The rate of symptomatic hypoglycaemic events was lower with lixisenatide (36%) compared to insulin glulisine QD and TID (47% and 52%, respectively).

FASTING PLASMA GLUCOSE

The mean decrease in fasting plasma glucose obtained with lixisenatide 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 lixisenatide resulted in reductions in 2-hour post-prandial glucose after a test-meal statistically superior to placebo, in placebo controlled studies. 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 with Lyxumia in combination with metformin and/or a sulphonylurea resulted in a sustained body weight change from baseline in all controlled studies in a range from -1.76 kg to -2.96 kg at the end of the main 24-week treatment period. Body weight reduction was sustained in long term studies up to 76 weeks.

Body weight change from baseline in a range from -0.38 kg to -1.80 kg was also observed in lixisenatide patients receiving stable basal insulin dose, alone or in combination with metformin or a sulphonylurea.

BETA CELL FUNCTION

In clinical studies, lixisenatide 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 lixisenatide.

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 randomised (randomisation 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%.

CARDIOVASCULAR OUTCOMES STUDY

The ELIXA study was a randomised, 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 hospitalisation for unstable angina. CV secondary endpoints included a composite of the primary endpoint, or hospitalisation for heart failure or coronary revascularisation. Changes in urinary albumin excretion at 108 weeks were also a pre-specified secondary endpoint. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio comparing lixisenatide to placebo.

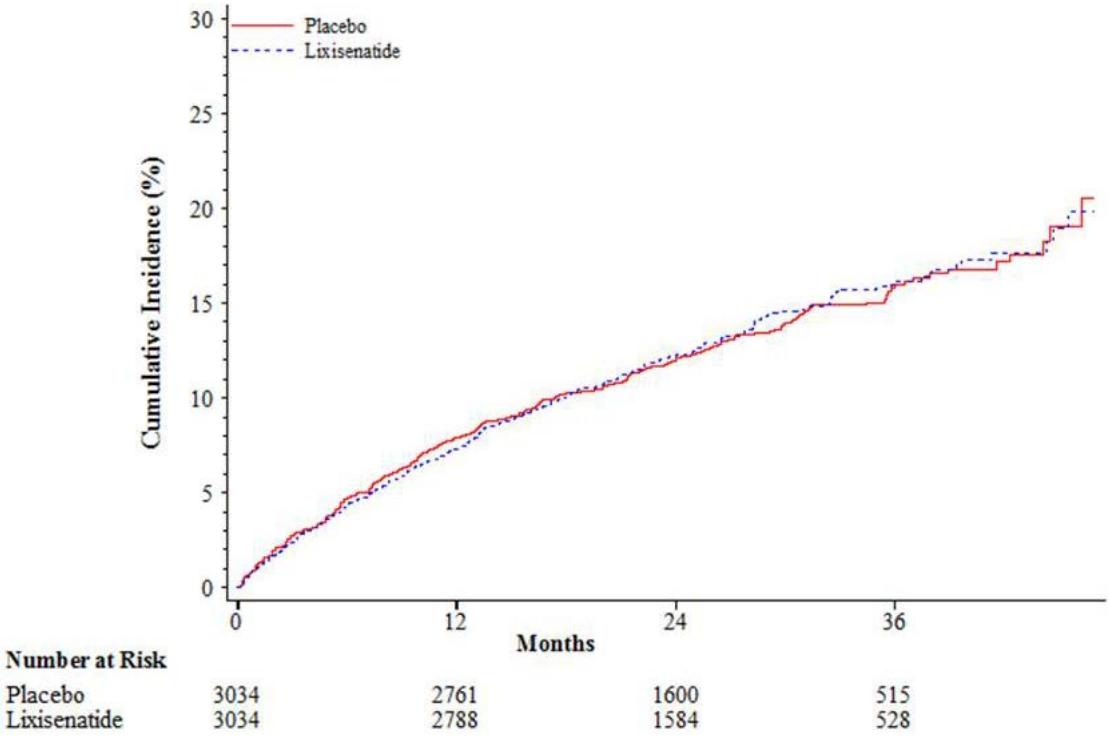
Overall, 6068 patients were randomised 1:1 to either placebo or lixisenatide 20 micrograms (following a starting dose of 10 micrograms during the first 2 weeks) and were included in the efficacy analyses. The demographics and baseline characteristics were well balanced between treatments. The median 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 greater than 30 and less than 60 mL/min/ 1.73 m^2. 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 one 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 3. 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.

The results from ELIXA, demonstrated that, with regard to CV safety, lixisenatide met non-inferiority but did not demonstrate superiority compared to placebo.

Figure 3 - 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 hospitalisation 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 3).

Table 8 - Analyses of each individual cardiovascular event – ITT population

	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				

	Placebo (N=3034) n (%)	Lixisenatide (N=3034) n (%)	Hazard ratio	95% CI
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

CV: cardiovascular, MI: myocardial infarction, HF: hospitalisation for heart failure, Revasc: coronary revascularisation procedure, HR: hazard ratio, CI: confidence interval. Only positively adjudicated events by the Cardiovascular Events Adjudication Committee are included.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each dose also contains glycerol (85%), sodium acetate, methionine, meta-cresol, hydrochloric acid/sodium hydroxide for pH adjustment, and water for injections.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, Lyxumia must not be mixed with other medicinal products.

6.3 SHELF LIFE

24 months when stored at 2° to 8° (Refrigerate, do not freeze).

After first use, Lyxumia must be kept at a temperature not exceeding 30°C. Do not refrigerate. The pen cap should be replaced on the pen after each use to protect it from light. The pen should not be stored with a needle attached.

The pen must be discarded 14 days after opening.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before first use, Lyxumia must be stored refrigerated between 2°C and 8°C in the outer packaging in order to protect it from light. Do not freeze.

Lyxumia should not be used if it has been frozen.

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

For storage conditions after first opening of the medicine, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Lyxumia is supplied as a sterile solution for subcutaneous injection in a 3mL glass cartridge that has been permanently integrated into a pre-filled injector pen.

Lyxumia is available as 2 different pens which deliver either a 10µg or 20µg dose of lixisenatide.

LYXUMIA 10µg solution for injection (green injection pen)

Solution for injection in a green pre-filled injector pen containing 3 mL solution delivering 14 doses of 10 µg. Supplied as a single (14 days supply) injector pen.

LYXUMIA 20µg solution for injection (purple injection pen)

Solution for injection in purple pre-filled injector pen containing 3 mL solution delivering 14 doses of 20 µg. Supplied in packs of 1 (14 days supply), 2 (28 days supply) and 6 (84 days supply) injector pens.

Lyxumia TREATMENT initiation pack (1 GREEN + 1 PURPLE INJECTION PEN)

Solution for injection composite pack containing 1 green pre-filled 10 µg pen (14 days supply), and 1 purple pre-filled 20 µg pen (14 days supply; 28 days total supply).

Lyxumia can be used with 29 to 32 gauge disposable pen needles. Pen needles are not included. The patient should be instructed to discard the needle after each use in accordance with local requirements and to store the pen without the needle attached. This helps prevent contamination and potential needle blockage.

Each Lyxumia pen is to be used for one patient only.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Lyxumia is supplied in Australia by:

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

Lyxumia is supplied in New Zealand by:

sanofi-aventis new zealand limited
Level 8,
56 Cawley Street, Ellerslie
Auckland
New Zealand
Freecall No: 0800 283 684

9 DATE OF FIRST APPROVAL

13 March 2014

10 DATE OF REVISION OF THE TEXT

9 June 2017

SUMMARY OF CHANGES

Section changed	Summary of new information
2	Added reference to excipients
4.1, 4.2, 4.4, 5.3	Updated section references
4.2	Updated administration instructions in relation to food as per CCDSv5 update
4.6	Updated headings according to DS template
4.8	Added reporting information for adverse events
5.1	Updated study information for 4-week study of effect of post-prandial glucose. Figure 1 graph title updated. Addition study information for 8 week study and Figure 2.
5.2	Renal impairment subsection updated to reflect Australian PI.
5.3	Table numbers updated. Additional data from clinical trials EFC12261, EFC12626, EFC11319 and EFC12703 added as per CCDSv5
6.3	Added shelf life as per TPDR
6.4	Added reference for storage conditions after opening
6.6	Added statement for disposal in accordance with local authorities
8	Updated address and added freecall number
9	Added date of first approval as per TPDR
10	Revision of text updated to: 9 June 2017