1. NAME OF THE MEDICINAL PRODUCT

Treatment initiation pack
Lyxumia 10 micrograms solution for injection
Lyxumia 20 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lyxumia 10 micrograms solution for injection
Each dose (0.2 ml) contains 10 micrograms (mcg) of lixisenatide (50 mcg per ml).

Lyxumia 20 micrograms solution for injection
Each dose (0.2 ml) contains 20 micrograms (mcg) of lixisenatide (100 mcg per ml).

Excipient(s) with known effects
Each dose contains 540 micrograms of metacresol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
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 oral glucose-lowering medicinal products and/or basal insulin when these, together, with diet and exercise, do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).

4.2 Posology and method of administration

Posology
Starting dose: dosing is initiated at 10 mcg lixisenatide once daily for 14 days.
Maintenance dose: a fixed maintenance dose of 20 mcg lixisenatide once daily is started on Day 15.

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 basal insulin, a reduction in the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia.
Lyxumia should not be given in combination with basal insulin and a sulphonylurea due to increased risk of hypoglycaemia (see section 4.4).
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
Elderly
No dose adjustment is required based on age.

Patients with renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment.
There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease and therefore, it is not recommended to use lixisenatide in these populations (see section 5.2).

Patients with hepatic impairment
No dose adjustment is needed in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of lixisenatide in children and adolescents less than 18 years of age have not yet been established. No data are available.

Method of administration
Lyxumia is to be injected subcutaneously in the thigh, abdomen or upper arm. Lyxumia should not be administered intravenously or intramuscularly.

The injection is administered once daily, within the hour prior to any meal of the day. 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 is missed, it should be injected within the hour prior to the next meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Acute pancreatitis
Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with lixisenatide although a causal relationship has not been established. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, lixisenatide should be discontinued ; if acute pancreatitis is confirmed, lixisenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

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

Renal impairment
There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease. Use is not recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Hypoglycaemia
Patients receiving Lyxumia with a sulphonylurea or with a basal insulin 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 (see section 4.2). Lixisenatide should not be given in combination with basal insulin and a sulphonylurea due to increased risk of hypoglycaemia.

Concomitant medicinal products
The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Lixisenatide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products are given in section 4.5.

Populations not studied
Lixisenatide has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors.

Dehydration
Patients treated with lixisenatide should be advised of the potential risk of dehydration in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Excipients
This medicinal product contains metacresol, which may cause allergic reactions.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products 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.
The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely, especially at the time of initiation of lixisenatide treatment. These medicinal products should be taken in a standardised way in relation to lixisenatide. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when lixisenatide is not administered.
For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before or 4 hours after lixisenatide injection.
Gastro-resistant formulations containing substances sensitive to stomach degradation, should be administered 1 hour before or 4 hours after lixisenatide injection.

Paracetamol
Paracetamol was used as a model medicinal product to evaluate the effect of lixisenatide on gastric emptying. Following administration of a single dose of paracetamol 1,000 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 10 mcg lixisenatide , C_{max} of paracetamol was decreased by 29% and 31% respectively and median t_{max} was delayed by 2.0 and 1.75 hours respectively. A further delay in t_{max} and a reduced C_{max} of paracetamol have been predicted with the 20 mcg maintenance dose.No effects on paracetamol C_{max} and t_{max} were observed when paracetamol was administered 1 hour before lixisenatide.
Based on these results, no dose adjustment for paracetamol is required but the delayed t_{max} observed when paracetamol is administered 1-4 hours after lixisenatide should be taken into account when a rapid onset of action is required for efficacy.

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 10 mcg lixisenatide, the C_{max}, AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel were unchanged.
Administration of the oral contraceptive 1 hour or 4 hours after lixisenatide did not affect AUC and $t_{1/2}$ of ethinylestradiol and levonorgestrel, 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 20 mcg and atorvastatin 40 mg were co-administered in the morning for 6 days, the exposure to atorvastatin was not affected, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours.
No such increase for t_{max} was observed when atorvastatin was administered in the evening and lixisenatide in the morning but the AUC and C_{max} of atorvastatin were increased by 27% and 66%, respectively.
These changes are not clinically relevant and therefore, no dose adjustment for atorvastatin is required when co-administered with lixisenatide.

Warfarin and other coumarin derivatives
After concomitant administration of warfarin 25 mg with repeated dosing of lixisenatide 20 mcg, 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 co-administered 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 20 mcg and digoxin 0.25 mg at steady state, the AUC of digoxin was not affected. The t_{max} of digoxin was delayed by 1.5 hour and the C_{max} was reduced by 26%.
Based on these results, no dose adjustment for digoxin is required when co-administered with lixisenatide.

Ramipril
After concomitant administration of lixisenatide 20 mcg and ramipril 5 mg during 6 days, the AUC of ramipril was increased by 21% while the C_{max} was decreased by 63%.The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2.5 hours.
Based on these results, no dose adjustment for ramipril is required when co-administered with lixisenatide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Lyxumia is not recommended in women of childbearing potential not using contraception.

Pregnancy
There are no adequate data from the use of Lyxumia in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Lyxumia should not be used during pregnancy. The use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Lyxumia should be discontinued.

Breast-feeding
It is unknown if Lyxumia is excreted in human milk. Lyxumia should not be used during breast-feeding.

Fertility
Animal studies do not indicate direct harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Lixisenatide has no or negligible influence on the ability to drive or use machines. 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

Summary of the safety profile
Over 2,600 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 studies were nausea, vomiting and diarrhoea. These reactions were mostly mild and transient.
In addition, hypoglycaemia (when Lyxumia was used in combination with a sulphonylurea and/or a basal insulin) and headache occurred.
Allergic reactions have been reported in 0.4% of Lyxumia patients.

Tabulated list of adverse reactions
Adverse reactions reported from placebo- and active-controlled phase III studies over the entire treatment period are presented in Table 1. The table presents adverse reactions 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 ≥1% in the Lyxumia group if the frequency was greater than 2 times the frequency for all comparators group.

Frequencies of adverse reactions are defined as: very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000).
Within each system organ class, adverse reactions are presented in order of decreasing frequency.

Table 1: Adverse reactions reported in placebo- and active-controlled phase III studies during the entire treatment period (including the period beyond the main 24-week treatment period in studies with ≥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 Vomiting Diarrhoea	Dyspepsia	
Skin and subcutaneous tissue disorders			Urticaria
Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions		Injection site pruritus	

Description of selected adverse reactions

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 lixisenatide 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 lixisenatide treated patients compared to 21.6% with placebo (25.6% absolute difference).

Overall, the incidence of severe symptomatic hypoglycaemia was uncommon (0.4% in lixisenatide patients and 0.2% in placebo patients) during the entire treatment period of the Phase III placebo-controlled studies.

Gastrointestinal disorders
Nausea and vomiting were the most frequently reported adverse reactions during the main 24-week treatment period. The incidence of nausea was higher in the lixisenatide group (26.1%) compared to the placebo group (6.2%) and the incidence of vomiting was higher in the lixisenatide group (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 were 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, 69.8% 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 HbA_{1c} from baseline was similar regardless of the antibody status (positive or negative). Of lixisenatide-treated patients with HbA1c measurement, 79.3% had either a negative antibody status or an antibody concentration below the lower limit of quantification and the other 20.7% of patients had a quantified antibody concentration. In the subset of patients (5.2%) with the highest antibody concentrations, the mean improvement in HbA_{1c} 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 HbA_{1c}.
The antibody status (positive or negative) is not predictive of the reduction of HbA_{1c} for an individual patient.

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). 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 possibly associated with lixisenatide (such as anaphylactic reaction, angioedema and urticaria) have been reported in 0.4% of lixisenatide patients while possibly associated allergic reactions occurred in less than 0.1% of 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
In a study in healthy volunteers, a transient rise in heart rate has been observed after administration of lixisenatide 20 mcg. 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 reactions which led to treatment discontinuation in the lixisenatide group were nausea (3.1%) and vomiting (1.2%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical studies, doses up to 30 mcg of lixisenatide twice a day were administered to type 2 diabetic patients in a 13 week study. 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 lixisenatide dose should be reduced to the prescribed dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in Diabetes, Glucagon-like peptide-1 (GLP-1) analogues , ATC code: A10BJ03.

Mechanism of action
Lixisenatide is a selective GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from 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 slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Pharmacodynamic effects
When administered once daily, lixisenatide improves glycaemic control through the immediate and sustained effects of lowering both post-prandial 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. Reduction from baseline in the $AUC_{0:30\text{-}4:30\ h}$ of plasma glucose after a test meal was: -12.61 h*mmol/L (-227.25 h*mg/dl) in the lixisenatide group and -4.04 h*mmol/L (-72.83 h*mg/dl) in the liraglutide group. This was also confirmed in an 8-week study versus liraglutide, administered before breakfast, in combination with insulin glargine with or without metformin.

Clinical efficacy and safety

The clinical efficacy and safety of Lyxumia were evaluated in nine randomised double-blind, placebo-controlled clinical studies including 4,508 patients with type 2 diabetes (2,869 patients randomised to lixisenatide, 47.5% men and 52.5% women, and 517 were ≥65 years of age).

Efficacy of Lyxumia was also assessed in two randomised, open-label, active-controlled study (versus exenatide or versus insulin glulisine) and in a meal time study (in total 1,067 patients randomised to lixisenatide).

Efficacy and safety of Lyxumia in patients older than 70 years was addressed in a specifically dedicated placebo-controlled study (176 patients randomised to lixisenatide, including 62 patients ≥75 years of age).

In addition, a double-blind, placebo-controlled cardiovascular outcome study (ELIXA) enrolled 6,068 type 2 diabetes patients with previous acute coronary syndrome (3,034 randomised to lixisenatide, including 198 patients ≥75 years of age and 655 patients with moderate renal impairment).

In the completed Phase III studies, it was observed that approximately 90% of the patients were able to remain on the once daily maintenance dose of 20 mcg Lyxumia at the end of the main 24-week treatment period.

- Glycaemic control

Add-on combination therapy with oral antidiabetics

Lyxumia in combination with metformin, a sulphonylurea, pioglitazone or a combination of these agents showed statistically significant reductions in HbA_{1c}, 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). The HbA_{1c} reduction was significant with once daily administration, whether administered morning or evening.
This effect on HbA_{1c} was sustained in long term studies for up to 76 weeks.

Add-on treatment to metformin alone

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

	Metformin as background therapy				
	Lixisenatide 20 mcg (N= 160)	Placebo (N= 159)	Lixisenatide 20 mcg		Placebo (N= 170)
			Morning (N= 255)	Evening (N= 255)	
Mean HbA_{1c} (%)					
Baseline	7.99	8.03	8.07	8.07	8.02
LS mean change from baseline	-0.92	-0.42	-0.87	-0.75	-0.38
Patients (%) achieving HbA_{1c} <7.0%	47.4	24.1	43.0	40.6	22.0
Mean body weight (kg)					
Baseline	90.30	87.86	90.14	89.01	90.40
LS mean change from baseline	-2.63	-1.63	-2.01	-2.02	-1.64

In an active-controlled study, Lyxumia once daily showed an HbA_{1c} reduction of -0.79% compared to -0.96% with exenatide twice daily at the end of the main 24-week treatment period with a mean treatment difference of 0.17% (95%CI: 0.033, 0.297) and a similar percentage of patients achieved an HbA_{1c} less than 7% in the lixisenatide group (48.5%) and in the exenatide group (49.8%).

The incidence of nausea was 24.5% in the lixisenatide group 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.

In a 24-week open-label study, lixisenatide administered before the main meal of the day was non-inferior to lixisenatide administered before breakfast in terms of HbA_{1c} reduction (LS mean change from baseline: -0.65% versus -0.74%). Similar HbA_{1c} decreases were observed regardless of which meal was the main meal (breakfast, lunch or dinner). At the end of the study, 43.6% (main meal group) and 42.8% (breakfast group) of patients achieved an HbA_{1c} less than 7%. Nausea was reported in 14.7% and 15.5% of patients, and symptomatic hypoglycaemia in 5.8% and 2.2% of patients, main meal group and breakfast group, respectively.

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

Table 3: Placebo-controlled study in combination with a sulphonylurea (24-week results)

	Sulphonylurea as background therapy with or without metformin	
	Lixisenatide 20 mcg (N= 570)	Placebo (N= 286)
Mean HbA_{1c} (%)		
Baseline	8.28	8.22
LS mean change from baseline	-0.85	-0.10
Patients (%) achieving HbA_{1c} <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 treatment to pioglitazone alone or in combination with metformin

In a clinical study, the addition of lixisenatide to pioglitazone with or without metformin, in patients not adequately controlled with pioglitazone, resulted in an HbA_{1c} decrease from baseline of 0.90%, compared to a decrease from baseline of 0.34% in the placebo group at the end of the 24-week main treatment period. At the end of the 24-week main treatment period, 52.3% of the lixisenatide patients achieved an HbA_{1c} less than 7% compared to 26.4% in the placebo group.
During the 24-week main treatment period, nausea was reported in 23.5% in the lixisenatide group compared to 10.6% in the placebo group and symptomatic hypoglycaemia was reported in 3.4% of the lixisenatide patients compared to 1.2% in the placebo group.

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 HbA_{1c} and in 2-hour post-prandial glucose after a test- meal compared to placebo.

Table 4: Placebo-controlled studies 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 mcg (N= 327)	Placebo (N= 166)	Lixisenatide 20 mcg (N= 154)	Placebo (N= 157)
Mean HbA_{1c} (%)				
Baseline	8.39	8.38	8.53	8.53
LS mean change from baseline	-0.74	-0.38	-0.77	0.11
Patients (%) achieving HbA_{1c} <7.0%	28.3	12.0	35.6	5.2
Mean duration of treatment with basal insulin at baseline (years)	3.06	3.2	2.94	3.01
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

A clinical study was conducted in insulin-naive patients insufficiently controlled on oral antidiabetic agents. This study consisted of a 12-week run-in period with introduction and titration of insulin glargine and of a 24-week treatment period during which patients receive either lixisenatide or placebo in combination with insulin glargine and metformin with or without thiazolidinediones. Insulin glargine was continuously titrated during this period.
During the 12-week run-in period, addition and titration of insulin glargine resulted approximately in an HbA_{1c} decrease of 1%. The addition of lixisenatide led to a significantly greater HbA_{1c} decrease of 0.71% in the lixisenatide group compared to 0.40% in the placebo group. At the end of the 24-week treatment period, 56.3% of the lixisenatide patients achieved an HbA_{1c} less than 7 % compared to 38.5% in the placebo group.
During the 24-week treatment period, 22.4% lixisenatide patients reported at least one symptomatic hypoglycaemic event compared to 13.5% in the placebo group. The incidence of hypoglycaemia was mainly increased in the lixisenatide group during the first 6 weeks of treatment and thereafter, was similar to the placebo group.

Patients with type 2 diabetes with basal insulin combined with 1-3 oral anti-diabetic agents were enrolled in an open-label randomised study for insulin intensification. After 12-week 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 level of HbA1c reduction was comparable between groups (table 5).

As opposed to both insulin glulisine treatment regimens, lixisenatide reduced body weight (table 5). The rate of symptomatic hypoglycaemic events was lower with lixisenatide (36%) compared to insulin glulisine QD and TID (47% and 52%, respectively).

Table 5: 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 HbA_{1c} (%)	N = 297	N = 298	N = 295
LS change from baseline	-0.63	-0.58	-0.84
LS mean difference (SE) of lixisenatide versus		-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 versus		-1.66 (0.305)	-1.99 (0.305)
95% CI		(-2.257 to -1.062)	(-2.593 to -1.396)*

*p<0.0001

- Fasting plasma glucose

The reductions in fasting plasma glucose obtained with Lyxumia treatment ranged from 0.42 mmol/L to 1.19 mmol/L (7.6 to 21.4 mg/dl) from baseline 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.
The reductions with Lyxumia ranged from 4.51 to 7.96 mmol/L (81.2 to 143.3 mg/dl) 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 (140.4 mg/dl).

- 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-weeks treatment period.
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.
In patients newly started on insulin, body weight remained almost unchanged in the lixisenatide group while an increase was shown in the placebo group.
Body weight reduction was sustained in long term studies up to 76 weeks.
The body weight reduction is independent from the occurrence of nausea and vomiting.

- Beta cell function

Clinical studies with Lyxumia indicate improved 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 were demonstrated in patients with type 2 diabetes (n=20) after a single dose of Lyxumia.

- Cardiovascular evaluation

No increase in mean heart rate patients with type 2 diabetes was seen in all placebo controlled phase III studies.

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

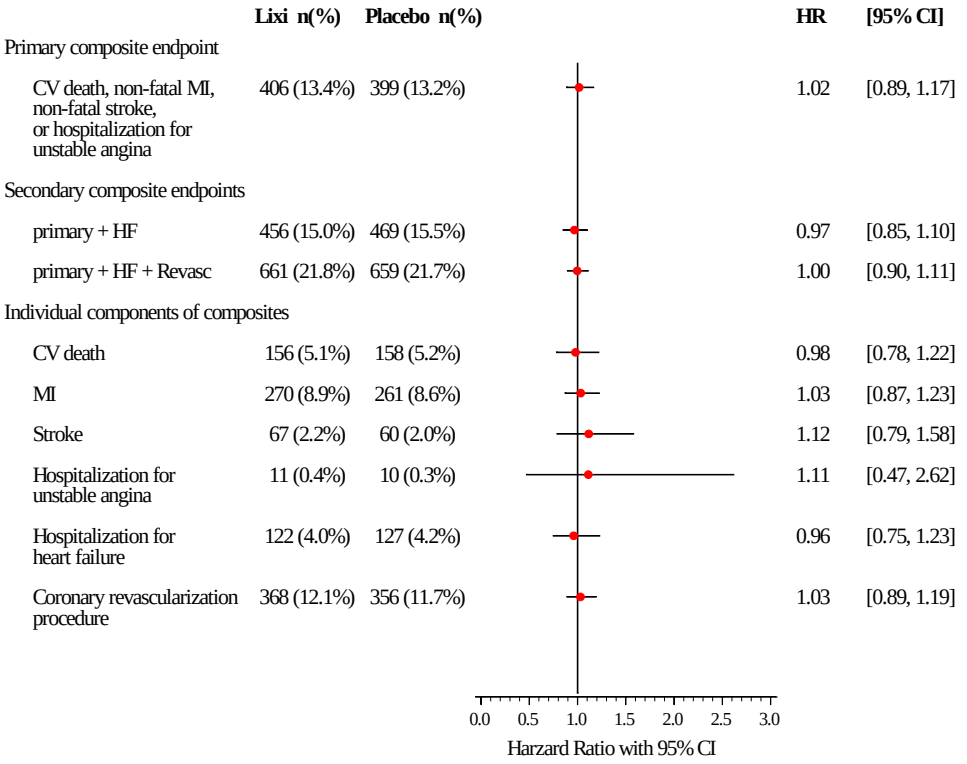
The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome.

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).

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 and secondary composite efficacy endpoints and the results of all the individual components of the composite endpoints are shown in Figure 1.

Figure 1: 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.

Elderly

People aged ≥70 years

The efficacy and safety of lixisenatide 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, patients with recent cardiovascular events 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%.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Lyxumia in one or more subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

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

Biotransformation and elimination
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.

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

Special populations
Patients with renal impairment
In subjects with mild (creatinine clearance calculated by the Cockcroft-Gault formula 60-90 ml/min), moderate (creatinine clearance 30-60 ml/min) and severe renal impairment (creatinine clearance 15-30 ml/min) AUC was increased by 46%, 51% and 87%, respectively.

Patients with 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.

Gender
Gender has no clinically relevant effect on the pharmacokinetics of lixisenatide.

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.

Elderly
Age has no clinically relevant effect on the pharmacokinetics of lixisenatide.
In a pharmacokinetic study in elderly non diabetic subjects, administration of lixisenatide 20 mcg resulted in a mean increase of lixisenatide AUC by 29% in the elderly population (11 subjects aged 65

to 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.

Body weight
Body weight has no clinically relevant effect on lixisenatide AUC.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology and toxicology.

In 2-year subcutaneous carcinogenicity studies, non-lethal C-cell thyroid tumours were seen in rats and mice and are considered to be caused by a non-genotoxic GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. C-cell hyperplasia and adenoma were seen at all doses in rats and a no observed adverse effect level (NOAEL) could be not defined. In mice, these effects occurred at exposure ratio above 9.3-fold when compared to human exposure at the therapeutic dose. No C-cell carcinoma was observed in mice and C-cell carcinoma occurred in rats with an exposure ratio relative to exposure at human therapeutic dose of about 900-fold. In 2-year subcutaneous carcinogenicity study in mice, 3 cases of adenocarcinoma in the endometrium were seen in the mid dose group with a statistically significant increase, corresponding to an exposure ratio of 97-fold. No treatment-related effect was demonstrated.

Animal studies did not indicate direct harmful effects with respect to male and female fertility in rats. Reversible testicular and epididymal lesions were seen in dogs treated with lixisenatide. No related effect on spermatogenesis was seen in healthy men.
In embryo-foetal development studies, malformations, growth retardation, ossification retardation and skeletal effects were observed in rats at all doses (5-fold exposure ratio compared to human exposure) and in rabbits at high doses (32-fold exposure ratio compared to human exposure) of lixisenatide. In both species, there was a slight maternal toxicity consisting of low food consumption and reduced body weight. Neonatal growth was reduced in male rats exposed to high doses of lixisenatide during late gestation and lactation, with a slightly increased pup mortality observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol 85%
Sodium acetate trihydrate
Methionine
Metacresol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide solution (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

After first use: 14 days

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store away from the freezer compartment.

After first use
Store below 30°C. Do not freeze.
Do not store with a needle attached. Keep the cap on the pen in order to protect from light.

6.5 Nature and contents of container

Treatment initiation pack
Type I glass cartridge with a (bromobutyl) rubber plunger, flanged caps (aluminium) with inserted laminated sealing disks (bromobutyl rubber on the inside and polyisoprene on the outside). Each cartridge is assembled into a disposable pen.

Pack containing 1 green pre-filled pen of Lyxumia 10 micrograms solution for injection and 1 purple pre-filled pen of Lyxumia 20 micrograms solution for injection.
Each green pre-filled pen contains 3 ml solution, delivering 14 doses of 10 mcg.
Each purple pre-filled pen contains 3 ml solution, delivering 14 doses of 20 mcg.

6.6 Special precautions for disposal and other handling

Lyxumia should not be used if it has been frozen.

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. The pen is to be used for one patient only.

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

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F – 75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/811/005 (1 pre-filled pen + 1 pre-filled pen)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 February 2013
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.