

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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.

For the starting dose Lyxumia 10 micrograms solution for injection is available.

For the maintenance dose Lyxumia 20 micrograms solution for injection is available.

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 been established (see section 5.1). 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 before 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 $\geq 1\%$ 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: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ 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	Rare
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		Delayed gastric emptying
Hepatobiliary disorders			Cholelithiasis Cholecystitis	
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

Injection 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 HbA_{1c} 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 $AUC_{0:30-4:30\text{ h}}$ 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 mealtime 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-naïve 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 HbA_{1c} 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-week 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 in 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.

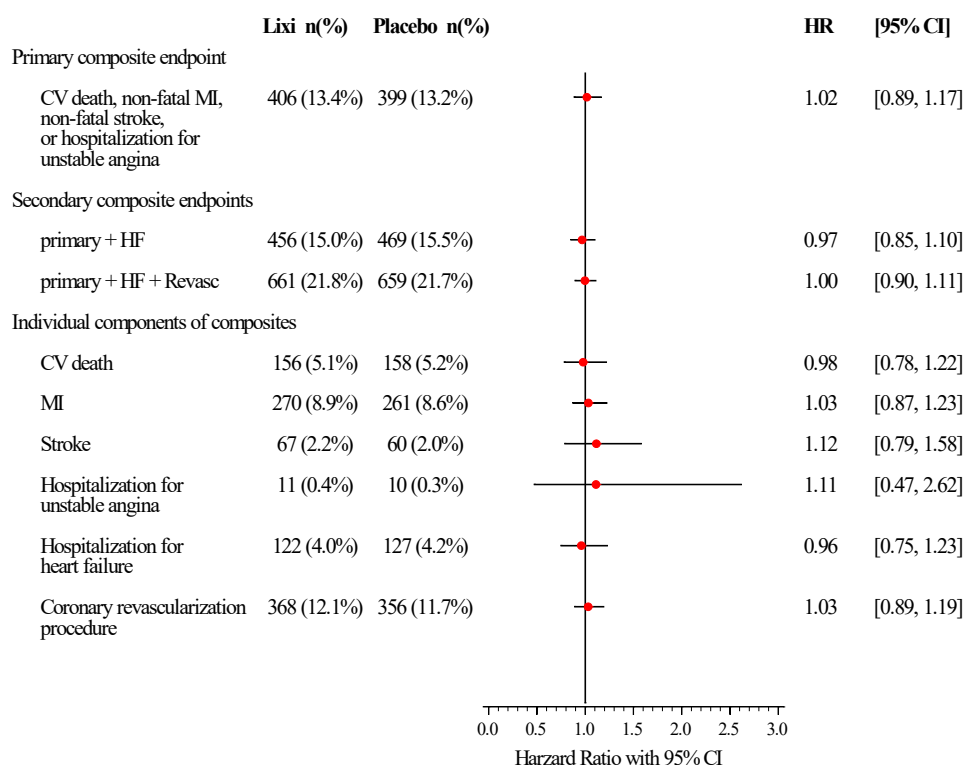
The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome.

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 (\pm SD) in the lixisenatide and placebo groups was 7.72 (\pm 1.32) % and 7.64 (\pm 1.28) % at baseline and 7.46 (\pm 1.51) % and 7.61 (\pm 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 \geq 70 years

The efficacy and safety of lixisenatide in people aged \geq 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 waived the obligation to submit the results of studies with Lyxumia in all 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 (V_z/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

3 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

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.

Lyxumia 10 micrograms solution for injection

Each green pre-filled pen contains 3 ml solution, delivering 14 doses of 10 mcg.

Pack containing 1 green pre-filled pen.

Lyxumia 20 micrograms solution for injection

Each purple pre-filled pen contains 3 ml solution, delivering 14 doses of 20 mcg.

Packs containing 1, 2 and 6 purple pre-filled pens.

Not all pack sizes may be marketed.

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 Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

Lyxumia 10 micrograms solution for injection

EU/1/12/811/001 (1 pre-filled pen)

Lyxumia 20 micrograms solution for injection

EU/1/12/811/002 (1 pre-filled pen)

EU/1/12/811/003 (2 pre-filled pens)

EU/1/12/811/004 (6 pre-filled pens)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 February 2013

Date of latest renewal: 18 September 2017

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>.

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 been established (see section 5.1). 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 before 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

Lyxisenatide 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 $\geq 1\%$ 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: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ 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	Rare
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		Delayed gastric emptying
Skin and subcutaneous tissue disorders			Urticaria	
Hepatobiliary disorders			Cholelithiasis Cholecystitis	
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

Injection 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 HbA_{1c} 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 $AUC_{0:30-4:30\text{ h}}$ of plasma glucose after a test meal was: $-12.61\text{ h}\cdot\text{mmol/L}$ ($-227.25\text{ h}\cdot\text{mg/dl}$) in the lixisenatide group and $-4.04\text{ h}\cdot\text{mmol/L}$ ($-72.83\text{ h}\cdot\text{mg/dl}$) 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 mealtime 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-naïve 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 HbA_{1c} 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.

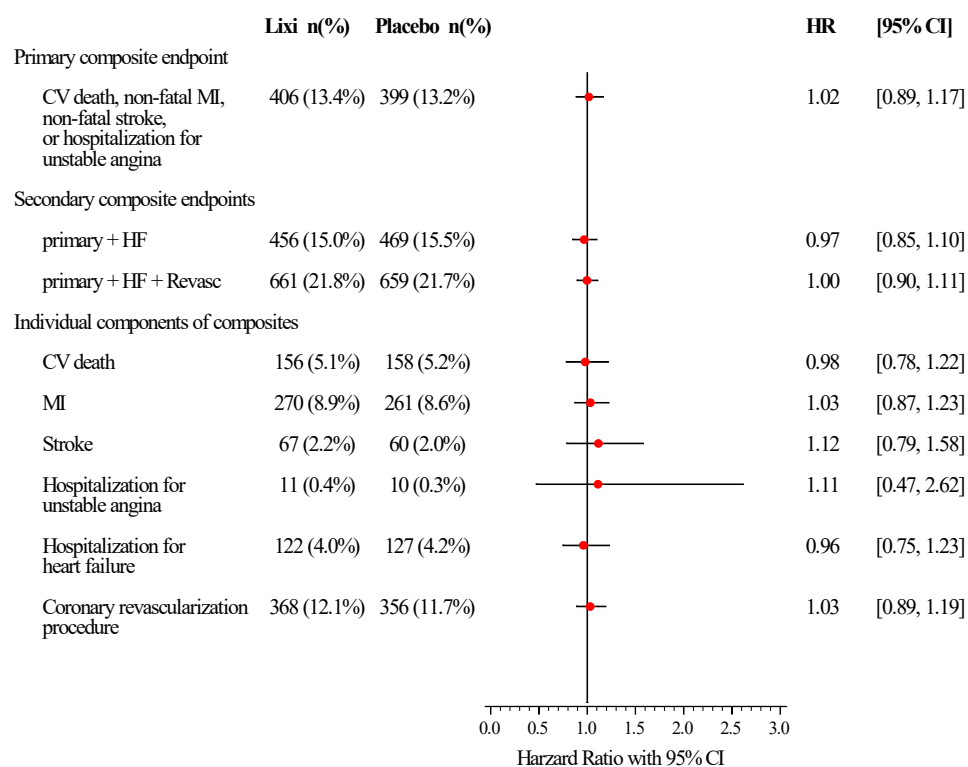
The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome.

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 (\pm SD) in the lixisenatide and placebo groups was 7.72 (\pm 1.32) % and 7.64 (\pm 1.28) % at baseline and 7.46 (\pm 1.51) % and 7.61 (\pm 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 waived the obligation to submit the results of studies with Lyxumia in all 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 (V_z/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

3 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 Winthrop Industrie
82 avenue Raspail
94250 Gentilly
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: 18 September 2017

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>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Sanofi-Aventis Deutschland GmbH
Brüningstrasse 50, Industriepark Höchst
65926 Frankfurt am Main
Germany

Name and address of the manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Brüningstrasse 50, Industriepark Höchst
65926 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (INITIATION PACK)

1. NAME OF THE MEDICINAL PRODUCT

Lyxumia 10 micrograms solution for injection
Lixisenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose (0.2 ml) contains 10 micrograms lixisenatide (50 micrograms per ml).

3. LIST OF EXCIPIENTS

Excipients: glycerol 85%, sodium acetate trihydrate, methionine, metacresol (see leaflet for further information), hydrochloric acid and sodium hydroxide solution (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen of 3 ml (14 doses)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard pen 14 days after first use

9. SPECIAL STORAGE CONDITIONS

Before first use
Store in a refrigerator. Do not freeze. Store away from the freezer compartment.

After first use

Store below 30°C. Do not freeze.

Keep the cap on the pen in order to protect from light.

Do not store with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/811/001 - 1 pen

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyxumia 10

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (MAINTENANCE PACK)

1. NAME OF THE MEDICINAL PRODUCT

Lyxumia 20 micrograms solution for injection
Lixisenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose (0.2 ml) contains 20 micrograms lixisenatide (100 micrograms per ml).

3. LIST OF EXCIPIENTS

Excipients: glycerol 85%, sodium acetate trihydrate, methionine, metacresol (see leaflet for further information), hydrochloric acid and sodium hydroxide solution (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen of 3 ml (14 doses)
2 pre-filled pens of 3 ml (2x14 doses)
6 pre-filled pens of 3 ml (6x14 doses)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard pen 14 days after first use

9. SPECIAL STORAGE CONDITIONS

Before first use

Store in a refrigerator. Do not freeze. Store away from the freezer compartment.

After first use

Store below 30°C. Do not freeze.

Keep the cap on the pen in order to protect from light.

Do not store with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/811/002 - 1 pen
EU/1/12/811/003 - 2 pens
EU/1/12/811/004 - 6 pens

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyxumia 20

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (28 DAYS TREATMENT INITIATION PACK)

1. NAME OF THE MEDICINAL PRODUCT

Lyxumia 10 micrograms solution for injection
Lyxumia 20 micrograms solution for injection
Lixisenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose (0.2 ml) contains 10 or 20 micrograms lixisenatide.

3. LIST OF EXCIPIENTS

Excipients: glycerol 85%, sodium acetate trihydrate, methionine, metacresol (see leaflet for further information), hydrochloric acid and sodium hydroxide solution (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Treatment initiation pack

Each pack of 2 pre-filled pens for a 4 week treatment schedule contains:

1 pre-filled pen of 3 ml for 14 doses of 10 micrograms

1 pre-filled pen of 3 ml for 14 doses of 20 micrograms

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

Printed on the inside:

Read the Instructions for Use carefully before using your Lyxumia pen.

You must start your treatment with the green pen of Lyxumia 10 micrograms.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard pen 14 days after first use

9. SPECIAL STORAGE CONDITIONS

Before first use

Store in a refrigerator. Do not freeze. Store away from the freezer compartment.

After first use

Store below 30°C. Do not freeze.

Keep the cap on the pen in order to protect from light.

Do not store with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/811/005 - 2 pens

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyxumia
10
20

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lyxumia 10 mcg injection
Lixisenatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml (14 doses)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lyxumia 20 mcg injection
Lixisenatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml (14 doses)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Lyxumia 10 micrograms solution for injection Lyxumia 20 micrograms solution for injection lixisenatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lyxumia is and what it is used for
2. What you need to know before you use Lyxumia
3. How to use Lyxumia
4. Possible side effects
5. How to store Lyxumia
6. Contents of the pack and other information

1. What Lyxumia is and what it is used for

Lyxumia contains the active substance lixisenatide.

It is an injectable medicine used to help your body to control your blood sugar level when it is too high. It is used in adults with type 2 diabetes.

Lyxumia is used with other medicines for diabetes when they are not enough to control your blood sugar levels. These may include:

- oral antidiabetics (such as metformin, pioglitazone, sulphonylurea medicines) and/or,
- a basal insulin, a type of insulin which works all day.

2. What you need to know before you use Lyxumia

Do not use Lyxumia

- if you are allergic to lixisenatide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Lyxumia if:

- you have type 1 diabetes or diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin) since this medicine will not be right for you
- you have or have had inflammation of the pancreas (pancreatitis)
- you have a severe stomach or gut problem such as a disease of the muscles of the stomach called “gastroparesis” which results in delayed stomach emptying
- you have severe kidney disease, or you are on dialysis as the use of this medicine will not be recommended

- you are also taking a sulphonylurea or a basal insulin. This is because low blood sugar (hypoglycaemia) can occur. Your doctor may want to control your blood sugar level and then, decide to reduce your dose of basal insulin or sulphonylurea. Lyxumia should not be used with a combination of both basal insulin and sulphonylurea
- you are taking other medicines, as there are other medicines such as antibiotics or stomach resistant tablets or capsules that should not stay too long in your stomach (see section Other medicines and Lyxumia)
- you experience loss of fluids/dehydration, e.g., in case of vomiting, nausea and diarrhoea. It is important to avoid dehydration by drinking plenty of fluids, especially when starting treatment with Lyxumia
- you suffer from heart problems which can cause shortness of breath or ankle swelling, since there is limited experience in this population.

Children and adolescents

There is no experience with Lyxumia in children and adolescents less than 18 years and therefore, the use of Lyxumia is not recommended in this age group.

Other medicines and Lyxumia

Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

The effect of some medicines you swallow might be affected by Lyxumia. Some medicines such as antibiotics or stomach resistant tablets or capsules that should not stay too long in your stomach may need to be taken at least one hour before or four hours after your Lyxumia injection.

Pregnancy and breast-feeding

Lyxumia should not be used during pregnancy. It is not known if Lyxumia may harm your unborn child.

Lyxumia should not be used if breast-feeding. It is not known if Lyxumia passes into your milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

If you use Lyxumia with a sulphonylurea or a basal insulin, you may get low blood sugar (hypoglycaemia). This may make it difficult to concentrate and you may feel dizzy or sleepy. If this happens do not drive or use any tools or machines.

Important information about some of the ingredients of Lyxumia

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially “sodium-free”.

This medicine contains metacresol which may cause allergic reactions.

3. How to use Lyxumia

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to inject

- The starting dose is 10 micrograms once a day for the first 14 days – injected using the **green** pen.
- The dose from then onwards will be 20 micrograms once a day -using the **purple** pen.

When to inject

Inject Lyxumia in the hour before any meal of the day. Preferably inject Lyxumia before the same meal every day, when you have chosen the most convenient meal for your injection.

Where to inject

Inject Lyxumia into the skin (subcutaneously) of your stomach area (abdomen), upper leg (thigh) or upper arm.

Learning how to use the pre-filled pens

Before you use the pen for the first time, your doctor or nurse will show how to inject Lyxumia.

- **Always read the "Instructions for Use" provided in the box.**
- **Always use the pen as described in the "Instructions for Use".**

Other important information about using the pre-filled pens

There is more information on how to use the pens in the "Instructions for Use". The most important points are:

- Always use a new needle for each injection. You must dispose of the needle after each use, in an appropriate sharp's container, following local recommendations. Speak to your doctor, nurse or pharmacist about how to dispose of sharps.
- Only use needles that are compatible for use with Lyxumia pen (see "Instructions for Use").
- **You must activate your Lyxumia pen before you use it for the first time.** This is to make sure that it is working correctly and that the dose for your first injection is correct.
- If you think your Lyxumia pen may be damaged, do not use it. Get a new one. Do not try to repair the pen.

If you use more Lyxumia than you should

If you use more Lyxumia than you should, talk to your doctor immediately. Too much Lyxumia can make you feel sick or be sick.

If you forget to use Lyxumia

If you miss a dose of Lyxumia, you can inject it in the hour before your next meal. Do not take two doses at the same time to make up for a forgotten injection.

If you stop using Lyxumia

Do not stop using Lyxumia without talking with your doctor. If you stop using Lyxumia, your blood sugar levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some severe allergic reactions (such as anaphylaxis) have been reported uncommonly in patients receiving Lyxumia. You should seek immediate medical attention if you experience symptoms like swelling of the face, tongue or throat which causes difficulty with breathing.

Stop taking Lyxumia and contact a doctor immediately if you notice any of the following serious side effects:

- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back, as well as nausea and vomiting, as it could be a sign of an inflamed pancreas (pancreatitis).

The most frequent side effects reported with Lyxumia that may affect more than 1 in 10 users (frequency very common) were nausea (feeling sick) and vomiting. These side effects were mostly mild and usually go away over time.

Other side effects include

Very common side effects: may affect more than 1 in 10 people

- Diarrhoea
- Headache
- Low blood sugar (hypoglycaemia (“hypo”)) especially when Lyxumia is used with insulin or a sulphonylurea

The warning signs of low blood sugar may include cold sweat, cool pale skin, headache, feeling drowsy, weak, dizzy, confused or irritable, feeling hungry, fast heartbeat and feeling jittery. Your doctor will tell you what to do if you get a low blood sugar.

This is more likely to happen if you also take a sulphonylurea or a basal insulin. Your doctor may reduce your dose of these medicines before you start using Lyxumia.

Common side effects: may affect up to 1 in 10 people

- Flu (influenza)
- Cold (upper respiratory tract infection)
- Feeling dizzy
- Indigestion (dyspepsia)
- Back pain
- Cystitis
- Viral infection
- Low blood sugar (when Lyxumia is taken with metformin)
- Drowsiness (somnolence)
- Injection site reactions (such as itching).

Uncommon side effect: may affect up to 1 in 100 people

- Hives (urticaria)
- Gallstones
- Inflamed gallbladder

Rare side effect: may affect up to 1 in 1,000 people

- A delay in the emptying of the stomach

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lyxumia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the carton after EXP. The expiry date refers to the last day of the month.

Before first use

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

During use of the pen

The pen can be used for 14 days when stored at a temperature below 30°C. Do not freeze. Do not store with a needle attached. When you are not using the pen, keep the cap on the pen in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lyxumia contains

- The active substance is lixisenatide.
- Lyxumia 10 micrograms solution for injection: Each dose contains 10 micrograms of lixisenatide (50 micrograms per ml).
- Lyxumia 20 micrograms solution for injection: Each dose contains 20 micrograms of lixisenatide (100 micrograms per ml).
- The other ingredients are glycerol 85 %, sodium acetate trihydrate, methionine, metacresol, hydrochloric acid (for pH adjustment), sodium hydroxide solution (for pH adjustment) and water for injections.

What Lyxumia looks like and contents of the pack

Lyxumia is a clear and colourless solution for injection (injection) filled in a glass cartridge inserted in a pre-filled pen.

Each green pen of Lyxumia 10 micrograms solution for injection contains 3 ml of solution, delivering 14 doses of 10 micrograms. Pack size of 1 pre-filled pen.

Each purple pen of Lyxumia 20 micrograms solution for injection contains 3 ml of solution, delivering 14 doses of 20 micrograms. Pack sizes of 1, 2 or 6 pre-filled pens. Not all pack sizes may be available in your country.

A treatment initiation pack is also available for use during the first 28 days of treatment. The treatment initiation pack contains one green pen of Lyxumia 10 micrograms solution for injection and one purple pen of Lyxumia 20 micrograms solution for injection.

Marketing Authorisation Holder

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturer

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst - 65926 Frankfurt am Main
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Lyxumia 10 micrograms solution for injection

Lixisenatide

INSTRUCTIONS FOR USE

Each pre-filled pen contains 14 doses, each dose contains **10 micrograms in 0.2 ml**.

Section 1 - IMPORTANT INFORMATION

Read these instructions carefully before using your Lyxumia pen.

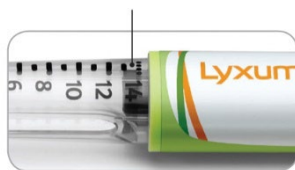
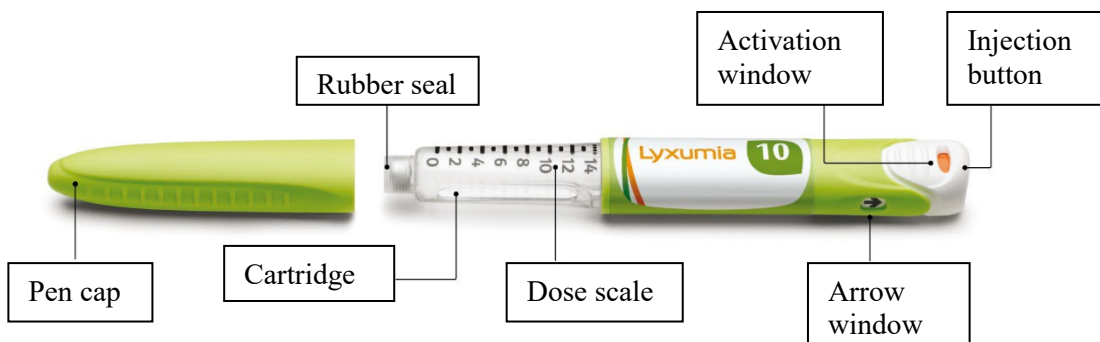
Keep this leaflet for future reference

Lyxumia pen Information

Lyxumia comes as a pre-filled pen for injection.

- **Only inject one dose per day.**
- Each Lyxumia pen contains 14 pre-set doses. There is no need to measure each dose.
- Talk with your doctor, pharmacist or nurse about how to inject correctly before using it.
- If you cannot follow all the instructions completely on your own or are not able to handle the pen (for example, if you have vision problems), only use it if you have help.

About Your Lyxumia Pen

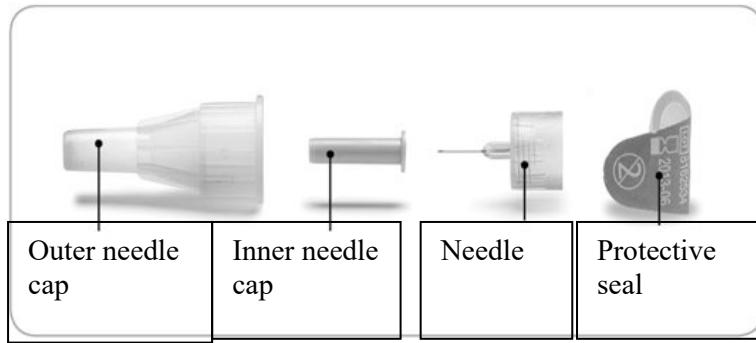


Black plunger

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

- This pen is only for one person. Do not share it with anyone else.
- Always check the label to ensure you have the correct Lyxumia pen. Also, check it has not passed the expiry date. Using the wrong medicine could be harmful to your health.
- Do not try to take liquid out of the cartridge using a syringe.

About your needle (supplied separately)



- Only use needles that are approved for use with Lyxumia. Use 29 to 32 gauge disposable pen needles with your Lyxumia pen. Ask your doctor, pharmacist or nurse which needle gauge and length is best for you.
- If another person is giving the injection, they should take care not to injure anyone accidentally with the needle. This could possibly pass on infection.
- Always use a new needle for each injection. This helps prevent contamination of Lyxumia or possible needle blockage.

Section 2 - GETTING STARTED

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

First activate your new pen

- **Before injecting a dose** - before injecting you must first remove excess liquid from your new pen. This is done once and is called the 'activation' process. Steps 1 to 5 below show you how to do this.
- Activation is done to make sure that the pen is working correctly and that the dose for your first injection is correct.
- **Do not repeat** the activation process or you will not obtain 14 doses from your Lyxumia pen.

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

New pen
(orange window)



Pen ready for injections
(white window)



The pen is activated and ready for injections. The window remains white after activation.

How to activate your new Lyxumia pen

Step 1 Pull off the pen cap and check the pen



Check the liquid. It should be clear and colourless with no particles. If not, do not use this pen.
Contact your doctor, pharmacist or nurse.

Check that the activation window is orange.

Step 2 Attach a needle and remove the needle caps



Always use a **new needle** for activation.
Remove the protective seal from the outer needle cap
Line up the needle with the pen. Keep it straight as you screw it on.



Take care not to injure yourself when the needle is exposed.
Pull off the outer and inner needle caps. Keep the outer needle cap - you will need it to remove the needle later.

Step 3 Pull injection button out



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4 Press and hold injection button to remove excess liquid



Point the needle into a suitable container (like a paper cup or tissue) to capture the liquid so that it can be thrown away.

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 in order to expel the last drops.



If no liquid comes out, see the “Questions and answers” section.
Check that the activation window is now white.

Step 5 The pen is now activated

Do not activate this pen again.

You **do not** need to replace the needle between activation and your first injection.
For your first injection go directly to Section 3 – Step C.

Turn over

Section 3 - DAILY USE OF PEN

Only follow this section when the activation window is white.
Inject only one dose each day.



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



Check the liquid. It should be clear and colourless with no particles. If not, do not use this pen. In case of air bubbles see the “Questions and answers” section.

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

Check that the activation window is white. If it is orange, go to Section 2.
Check the label on your pen to make sure you have the correct medicine.

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



Always use a **new needle** for each injection.
Remove protective seal from the outer needle cap.
Line up the needle with the pen. Keep it straight as you screw it on.



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

Pull off the outer and inner needle caps. Keep the outer needle cap - you will need it to remove the needle later.

Step C. Pull the injection button out



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

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



Grasp a fold of skin and insert the needle (see the “Injection sites” section about where to inject).

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 to get the full dose.

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

Step E. Remove and throw away the needle after each injection



Put the outer needle cap on a flat surface. Guide the needle into the outer needle cap. Put the outer needle cap back on.



Squeeze the outer needle cap to grip the needle and use it to unscrew the needle from the pen.



Ask your pharmacist how to throw away the needle you no longer use.
Replace the pen cap

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

Throw away a pen 14 days after activation. Do this even if there is some medicine left in the pen.

Table of activation and disposal

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

Pen	Date of activation	Date to discard
1		

Storage

General information

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

Before activation of the pen:

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

After activation of the pen:

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

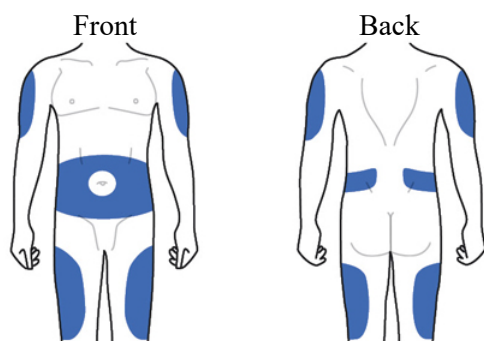
Disposal

- Replace the pen cap before you throw away your Lyxumia pen.
- Throw away your Lyxumia pen, ask your pharmacist how to throw away medicines you no longer use.

Maintenance

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

Injection sites



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

Questions and answers

What if I forget to activate the Lyxumia pen or inject myself before activation?

If you have injected yourself before activating the pen, do not correct this by giving yourself a second injection. Contact your doctor, pharmacist or nurse for advice on checking your blood sugar.

What if there are air bubbles in the container?

Small air bubbles in the container are normal - they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your doctor, pharmacist or nurse if you need help.

What if no liquid comes out during activation?

The needle may be blocked or not properly screwed on. Remove the needle from the pen, attach a new one and repeat Steps 4 and 5 only. If still no liquid comes out, your Lyxumia pen may be damaged. Do not use this Lyxumia pack. Contact your doctor, pharmacist or nurse for help.

What if it is hard to press the injection button all the way in?

The needle may be blocked or not properly screwed on. Pull the needle out of your skin and remove the needle from the pen. Attach a new needle and repeat Steps D and E only. If it is still hard to press the injection button, your Lyxumia pen may be damaged. Do not use this Lyxumia pack. Contact your doctor, pharmacist or nurse for help.

If you have any questions about Lyxumia or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned in the Lyxumia “Package leaflet: Information for the user” (provided separately in the box).

Lyxumia 20 micrograms solution for injection

Lixisenatide

INSTRUCTIONS FOR USE

Each pre-filled pen contains 14 doses, each dose contains **20 micrograms in 0.2 ml**.

Section 1 - IMPORTANT INFORMATION

Read these instructions carefully before using your Lyxumia pen.

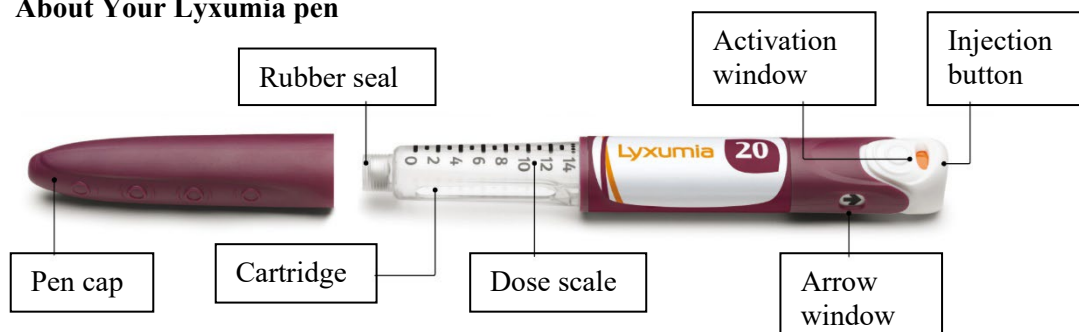
Keep this leaflet for future reference

Lyxumia pen Information

Lyxumia comes as a pre-filled pen for injection.

- **Only inject one dose per day.**
- Each Lyxumia pen contains 14 pre-set doses. There is no need to measure each dose.
- Talk with your doctor, pharmacist or nurse about how to inject correctly before using it.
- If you cannot follow all the instructions completely on your own or are not able to handle the pen (for example, if you have vision problems), only use it if you have help.

About Your Lyxumia pen

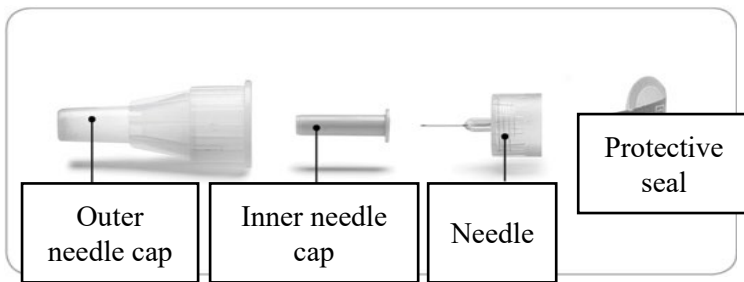


Black plunger

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

- This pen is only for one person. Do not share it with anyone else.
- Always check the label to ensure you have the correct Lyxumia pen. Also, check it has not passed the expiry date. Using the wrong medicine could be harmful to your health.
- Do not try to take liquid out of the cartridge using a syringe.

About your needle (supplied separately)



- Only use needles that are approved for use with Lyxumia. Use 29 to 32 gauge disposable pen needles with your Lyxumia pen. Ask your doctor, pharmacist or nurse which needle gauge and length is best for you.
- If another person is giving the injection, they should take care not to injure anyone accidentally with the needle. This could possibly pass on infection.
- Always use a new needle for each injection. This helps prevent contamination of Lyxumia or possible needle blockage.

Section 2 - GETTING STARTED

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

First activate your new pen

- **Before injecting a dose** - before injecting you must first remove excess liquid from your new pen. This is done once and is called the 'activation' process. Steps 1 to 5 below show you how to do this.
- Activation is done to make sure that the pen is working correctly and that the dose for your first injection is correct.
- **Do not repeat** the activation process or you will not obtain 14 doses from your Lyxumia pen.

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

New pen
(orange window)



Pen ready for injections
(white window)



The pen is activated and ready for injections. The window remains white after activation.

How to activate your new Lyxumia pen

Step 1 Pull off the pen cap and check the pen



Check the liquid. It should be clear and colourless and with no particles. If not, do not use this pen. Contact your doctor, pharmacist or nurse.

Check that the activation window is orange

Step 2 Attach a needle and remove the needle caps



Always use a **new needle** for activation.
Remove the protective seal from the outer needle cap.
Line up the needle with the pen. Keep it straight as you screw it on.



Take care not to injure yourself when the needle is exposed.
Pull off the outer and inner needle caps. Keep the outer needle cap – you will need it to remove the needle later.

Step 3 Pull injection button out



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4 Press and hold the injection button to remove excess liquid



Point the needle into a suitable container (like a paper cup or tissue) to capture the liquid so that it can be thrown away.

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 in order to expel the last drops.



If no liquid comes out, see the “Questions and answers” section.
Check that the activation window is now white.

Step 5 The pen is now activated.

Do not activate this pen again.

You **do not** need to replace the needle between activation and your first injection.

For your first injection go directly to Section 3 - Step C.

Turn over

Section 3 - DAILY USE OF PEN

Only follow this section when the activation window is white.

Inject only one dose each day.



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



Check the liquid. It should be clear and colourless with no particles. If not, do not use this pen.

In case of air bubbles see the “Questions and answers” section.

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

Check that the activation window is white. If it is orange, go to Section 2.

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

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



Always use a **new needle** for each injection.

Remove the protective seal from the outer needle cap.

Line up the needle with the pen. Keep it straight as you screw it on.



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

Pull off the outer and inner needle caps. Keep the outer needle cap – you will need it to remove the needle later.

Step C. Pull the injection button



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

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



Grasp a fold of skin and insert the needle (see the “Injection sites” section about where to inject).

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 to get the full dose.

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

Step E. Remove and throw away needle after each injection



Put the outer needle cap on a flat surface. Guide the needle into the outer needle cap. Put the outer needle cap back on.



Squeeze the outer needle cap to grip the needle and use it to unscrew the needle from the pen.



Ask your pharmacist how to throw away the needle you no longer use.
Replace the pen cap.

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

Throw away a pen 14 days after activation. Do this even if there is some medicine left in the pen.

Table of activation and disposal

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

Pen	Date of activation	Date to discard
1		
2		
3		
4		
5		
6		

Storage

General information

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

Before activation of the pen:

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

After activation of the pen:

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

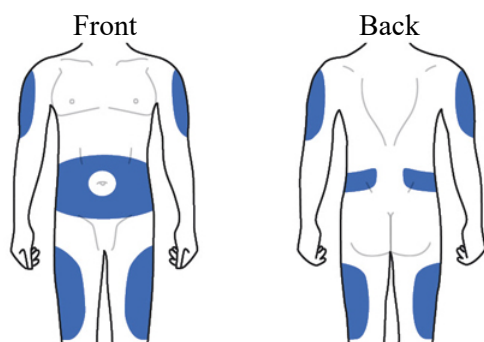
Disposal

- Replace the pen cap before you throw away your Lyxumia pen.
- Throw away your Lyxumia pen, ask your pharmacist how to throw away medicines you no longer use.

Maintenance

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

Injection sites



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

Questions and answers

What if I forget to activate the Lyxumia pen or inject myself before activation?

If you have injected yourself before activating the pen, do not correct this by giving yourself a second injection. Contact your doctor, pharmacist or nurse for advice on checking your blood sugar.

What if there are air bubbles in the container?

Small air bubbles in the container are normal - they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your doctor, pharmacist or nurse if you need help.

What if no liquid comes out during activation?

The needle may be blocked or not properly screwed on. Remove the needle from the pen, attach a new one and repeat Steps 4 and 5 only. If still no liquid comes out, your Lyxumia pen may be damaged. Do not use this Lyxumia pack. Contact your doctor, pharmacist or nurse for help.

What if it is hard to press the injection button all the way in?

The needle may be blocked or not properly screwed on. Pull the needle out of your skin and remove the needle from the pen. Attach a new needle and repeat Steps D and E only. If it is still hard to press the injection button, your Lyxumia pen may be damaged. Do not use this Lyxumia pack. Contact your doctor, pharmacist or nurse for help.

If you have any questions about Lyxumia or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned in the Lyxumia "Package leaflet: Information for the user" (provided separately in the box).

Lyxumia

Lixisenatide

INSTRUCTIONS FOR USE

Treatment Initiation pack - Contains two pre-filled pens each with **14** doses.

One green **10 microgram** pen (Lyxumia 10 micrograms solution for injection), each dose contains **10 micrograms in 0.2 ml**.

One purple **20 microgram** pen (Lyxumia 20 micrograms solution for injection), each dose contains **20 micrograms in 0.2 ml**.

Section 1 - IMPORTANT INFORMATION

Read these instructions carefully before using your Lyxumia pens.

Keep this leaflet for future reference.

Lyxumia pen Information

- **Only inject one dose per day.**
- Each Lyxumia pen contains 14 pre-set doses. There is no need to measure each dose.
- Talk with your doctor, pharmacist or nurse about how to inject correctly before using it.
- If you cannot follow all the instructions completely on your own or are not able to handle the pen (for example, if you have vision problems), only use it if you have help.

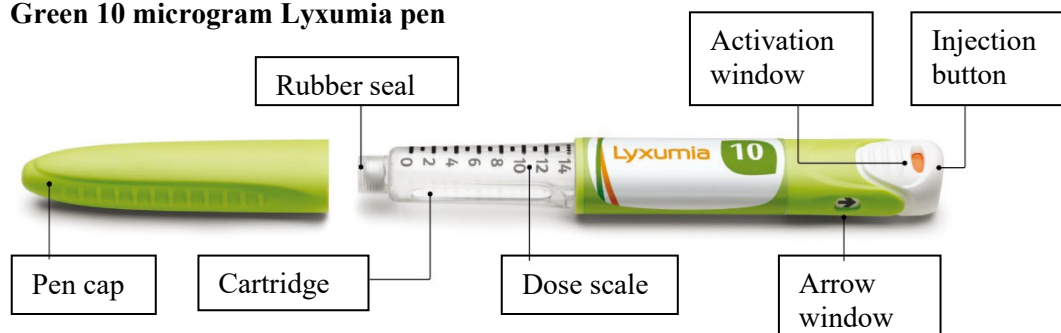
About Your Treatment Initiation pack

The Lyxumia Treatment Initiation pack includes two different coloured pens. Each pen contains a different strength of Lyxumia. Both pens are used in the same way.

- The green pen contains 14 pre-set doses; each dose contains 10 micrograms of Lyxumia.
 - The purple pen contains 14 pre-set doses; each dose contains 20 micrograms of Lyxumia.
- You must start your treatment with the green 10 micrograms Lyxumia pen. You must first use all 14 doses from this pen. Then use the purple 20 micrograms Lyxumia pen.

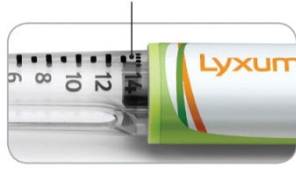
About Your Lyxumia pens

Green 10 microgram Lyxumia pen



Purple 20 microgram Lyxumia pen



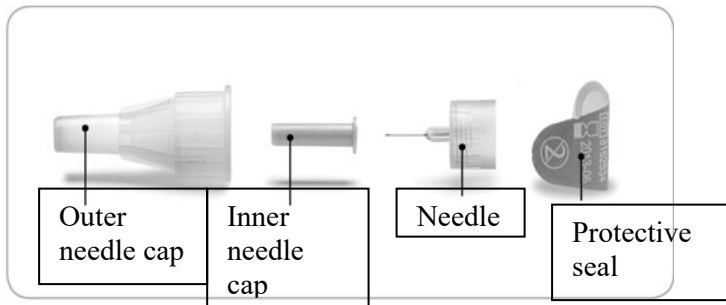


Black plunger

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

- These pens are only for one person. Do not share them with anyone else.
- Always check the label to ensure you have the correct Lyxumia pen. Also check it has not passed the expiry date. Using the wrong medicine could be harmful to your health.
- Do not try to take liquid out of the cartridge using a syringe.

About your needle (supplied separately)



- Only use needles that are approved for use with Lyxumia. Use 29 to 32 gauge disposable pen needles with your Lyxumia pen. Ask your doctor, pharmacist or nurse which needle gauge and length is best for you.
- If another person is giving the injection, they should take care not to injure anyone accidentally with the needle. This could possibly pass on infection.
- Always use a new needle for each injection. This helps prevent contamination of Lyxumia or possible needle blockage.

Section 2 – GETTING STARTED

Begin with the green 10 microgram Lyxumia pen.

- **Do not activate the purple 20 microgram Lyxumia pen until you have finished the green pen.**
- **Activate the pen on the same day as your first injection.**

First activate your new pen

- **Before injecting a dose** - before injecting you must first remove excess liquid from your new pen. This is done once and is called the 'activation' process. Steps 1 to 5 below show you how to do this.
- Activation is done to make sure that the pen is working correctly and that the dose for your first injection is correct.
- **Do not repeat** the activation process or you will not obtain 14 doses from your Lyxumia pen.

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

New pen
(orange window)



Pen ready for injections
(white window)



The pen is activated and ready for injections. The window remains white after activation.

How to activate your new Lyxumia pen

Step 1 Pull off the pen cap and check the pen



Check the liquid. It should be clear and colourless with no particles. If not, do not use this Treatment Initiation pack. Contact your doctor, pharmacist or nurse.

Check that the activation window is orange.

Step 2 Attach a needle and remove the needle caps



Always use a **new needle** for activation.
Remove the protective seal from the outer needle cap.
Line up the needle with the pen. Keep it straight as you screw it on.



Take care not to injure yourself when the needle is exposed.
Pull off the outer and inner needle caps. Keep the outer needle cap – you will need it to remove the needle later.

Step 3 Pull the injection button out



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

Step 4 Press and hold the injection button to remove excess liquid



Point the needle into a suitable container (like a paper cup or tissue) to capture the liquid so that it can be thrown away.

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 in order to expel the last drops.



If no liquid comes out, see the “Questions and answers” section.

Check that the activation window is now white.

Step 5 The pen is now activated.

Do not activate this pen again.

You **do not** need to replace the needle between activation and your first injection.

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

Turn over

Section 3 - DAILY USE OF PEN

Only follow this section when the activation window is white.

Inject only one dose each day.



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



Check the liquid. It should be clear and colourless with no particles. If not, do not use this Treatment Initiation pack.

In case of air bubbles see the “Questions and answers” section.

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

Check that the activation window is white. If it is orange, go to Section 2.

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

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



Always use a **new needle** for each injection.

Remove the protective seal from the outer needle cap

Line up the needle with the pen. Keep it straight as you screw on.



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

Pull off the outer and inner needle caps. Keep the outer needle cap – you will need it to remove the needle later.

Step C. Pull the injection button out



Pull the injection button out firmly until it stops.



The arrow will now be pointing towards the needle.

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



Grasp a fold of skin and insert the needle (see the “Injection sites” section about where to inject).

Press the injection button all the way in. You may feel or hear a “click”.

Keep the injection button pressed in and slowly count to 5 to get the full dose.

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

Step E. Remove and throw away the needle after each injection



Put the outer needle cap on a flat surface. Guide the needle into the outer needle cap.
Put the outer needle cap back on.



Squeeze the outer needle cap to grip the needle and use it to unscrew the needle from the pen.



Ask your pharmacist how to throw away the needle you no longer use.
Replace the pen cap.

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

Throw away a pen 14 days after activation. Do this even if there is some medicine left in the pen.

Once you have thrown away the green pen continue to **Section 4** to begin using the purple pen.

Section 4 – MOVING TO THE PURPLE PEN

Completed use of the green 10 microgram pen



The green 10 micrograms Lyxumia pen is empty when the black plunger has reached '0' on the dose scale and the injection button cannot be pulled out fully.

Once the green 10 micrograms Lyxumia pen is empty you must continue your treatment by taking your next injection when it is due, using the purple 20 microgram Lyxumia pen. This is used in exactly the same way. **Use of purple 20 micrograms pen**



Purple 20 micrograms pen activation

The purple 20 micrograms Lyxumia pen must also be activated before use. Follow all steps in Section 2.

Purple 20 microgram pen Use

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

Table of activation and disposal

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

Pen	Date of activation	Date to throw away
10 microgram	___ / ___ / ___	___ / ___ / ___
20 microgram	___ / ___ / ___	___ / ___ / ___

Storage

General information

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

Before activation of the pen:

- Store your unused Lyxumia pens in the refrigerator, 2°C to 8°C.

- Do not freeze Lyxumia pens and do not use Lyxumia if it has been frozen.
- Allow your pen to warm at room temperature before using.

After activation of the pen:

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

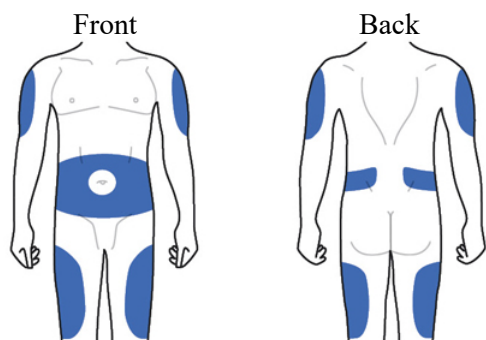
Disposal

- Replace the pen cap before you throw away your Lyxumia pen.
- Throw away your Lyxumia pen, ask your pharmacist how to throw away medicines you no longer use.

Maintenance

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

Injection sites



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

Questions and answers

What if I forget to activate the Lyxumia pen or inject myself before activation?

If you have injected yourself before activating the pen, do not correct this by giving yourself a second injection. Contact your doctor, pharmacist or nurse for advice on checking your blood sugar.

What if there are air bubbles in the container?

Small air bubbles in the container are normal - they will not harm you. Your dose will be correct and you can keep following the instructions. Contact your doctor, pharmacist or nurse if you need help.

What if no liquid comes out during activation?

The needle may be blocked or not properly screwed on. Remove the needle from the pen, attach a new one and repeat Steps 4 and 5 only. If still no liquid comes out, your Lyxumia pen may be damaged. Do not use this Lyxumia Treatment Initiation pack. Contact your doctor, pharmacist or nurse for help.

What if it is hard to press the injection button all the way in?

The needle may be blocked or not properly screwed on. Pull the needle out of your skin and remove the needle from the pen. Attach a new needle and repeat Steps D and E only. If it is still hard to press the injection button, your Lyxumia pen may be damaged. Do not use this Lyxumia Treatment Initiation pack. Contact your doctor, pharmacist or nurse for help.

If you have any questions about Lyxumia or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned in the Lyxumia “Package leaflet: Information for the user” (provided separately in the box).