

Lyxumia 10 micrograms solution for injection

Lyxumia 20 micrograms solution for injection

1. Name of the medicinal product

Lyxumia 10 mcg solution for injection

Lyxumia 20 mcg solution for injection

2. Qualitative and quantitative composition

Lyxumia 10 mcg

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

Lyxumia 20 mcg

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, colorless solution.

4. Clinical particulars

4.1 Therapeutic indications

Lyxumia is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycemic 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 Lyxumia once daily for 14 days.

Maintenance dose: a fixed maintenance dose of 20 mcg Lyxumia once daily is started on Day 15. Lyxumia 20 micrograms solution for injection is available for the maintenance dose.

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

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

When Lyxumia is added to 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 hypoglycemia. Lyxumia should not be given in combination with basal insulin and a sulphonylurea due to increased risk of hypoglycemia (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 patients (≥65 years)

No dose adjustment is required based on age. The clinical experience in patients ≥75 years is limited (see sections 5.1 and 5.2).

Patients with renal impairment

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

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

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 Lyxumia 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)

Pediatric population

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

Method of administration

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

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 limited therapeutic experience in patients with moderate renal impairment (creatinine clearance: 30-50 ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease. Lyxumia should be used with caution in patients with moderate renal impairment. Use is not recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Hypoglycemia

Patients receiving Lyxumia with a sulphonylurea or with a basal insulin may have an increased risk of hypoglycemia. Reduction of the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycemia (see section 4.2). Lyxumia should not be given in combination with basal insulin and a sulphonylurea due to increased risk of hypoglycemia.

Concomitant medicinal products

The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Lyxumia 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.

There is limited experience in patients with congestive heart failure.

Dehydration

Patients treated with Lyxumia 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.

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 1000 mg, paracetamol AUC and $t_{1/2}$ were unchanged whatever the timing of its administration (before or after the lixisenatide injection). When administered 1 or 4 hours after 10 mcg lixisenatide, C_{max} of paracetamol was decreased by 29% and 31% respectively and median t_{max} was delayed by 2.0 and 1.75 hours respectively. A further delay in t_{max} and a reduced C_{max} of paracetamol have been predicted with the 20 mcg maintenance dose.

No effects on paracetamol C_{max} and t_{max} were observed when paracetamol was administered 1 hour before lixisenatide.

Based on these results, no dose adjustment for paracetamol is required but the delayed t_{max} observed when paracetamol is administered 1-4 hours after lixisenatide should be taken into account when a rapid onset of action is required for efficacy.

Oral contraceptives

Following administration of a single dose of an oral contraceptive medicinal product (ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg) 1 hour before or 11 hours after 10 mcg lixisenatide, the C_{max} , AUC, $t_{1/2}$ and t_{max} of ethinylestradiol and levonorgestrel were unchanged.

Administration of the oral contraceptive 1 hour or 4 hours after lixisenatide did not affect AUC and $t_{1/2}$ of ethinylestradiol and levonorgestrel, whereas C_{max} of ethinylestradiol was decreased by 52% and 39% respectively and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively and median t_{max} was delayed by 1 to 3 hours.

The reduction in C_{max} is of limited clinical relevance and no dose adjustment for oral contraceptives is required.

Atorvastatin

When lixisenatide 20 mcg and atorvastatin 40 mg were co-administered in the morning for 6 days, the exposure to atorvastatin was not affected, while C_{max} was decreased by 31% and t_{max} was delayed by 3.25 hours.

No such increase for t_{max} was observed when atorvastatin was administered in the evening and lixisenatide in the morning but the AUC and C_{max} of atorvastatin were increased by 27% and 66% respectively.

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

Warfarin and other coumarin derivatives

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

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

Digoxin

After concomitant administration of lixisenatide 20 mcg and digoxin 0.25 mg at steady state, the AUC of digoxin was not affected. The t_{max} of digoxin was delayed by 1.5 hour and the C_{max} was reduced by 26%.

Based on these results, no dose adjustment for digoxin is required when co-administered with lixisenatide.

Ramipril

After concomitant administration of lixisenatide 20 mcg and ramipril 5 mg during 6 days, the AUC of ramipril was increased by 21% while the C_{max} was decreased by 63%. The AUC and C_{max} of the active metabolite (ramiprilat) were not affected. The t_{max} of ramipril and ramiprilat were delayed by approximately 2.5 hours.

Based on these results, no dose adjustment for ramipril is required when co-administered with lixisenatide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Lyxumia 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 hypoglycemia 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 diarrhea. These reactions were mostly mild and transient.

In addition, hypoglycemia (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
Infections and infestations		Influenza	
		Upper respiratory tract infection	
		Cystitis	
		Viral infection	
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycemia (in combination with a sulphonylurea and / or a basal insulin)	Hypoglycemia (in combination with metformin alone)	
Nervous system disorders	Headache	Dizziness	
		Somnolence	
Gastrointestinal disorders	Nausea	Dyspepsia	
	Vomiting		
	Diarrhea		
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

Hypoglycemia

In patients taking Lyxumia in monotherapy, symptomatic hypoglycemia 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 hypoglycemia 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 hypoglycemia 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 hypoglycemia 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 hypoglycemia 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 hypoglycemia occurred in 47.2% of lixisenatide treated patients compared to 21.6% with placebo (25.6% absolute difference).

Overall, the incidence of severe symptomatic hypoglycemia 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%).

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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.HEALTH.GOV.IL).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other blood glucose lowering drugs, excl. insulins, ATC code: **A10BX10**.

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 hypoglycemia. In parallel, glucagon secretion is suppressed. In case of hypoglycemia, 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 glycemic 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 h} of plasma glucose after a test-meal was: -12.61 h*mmol/L (-227.25 h*mg/dl) (~~12.61 h*mmol/L~~) in the lixisenatide group and -4.04 h*mmol/L (-72.83 h*mg/dl) (~~-4.04 h*mmol/L~~) 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 effects of Lyxumia on glycemic control were evaluated in six randomised double-blind, placebo-controlled clinical studies and one randomised, open-label, active-controlled study versus exenatide.

These studies included 3,825 patients with type 2 diabetes (2,445 patients randomised to lixisenatide), 48.2% men and 51.8% women.

768 subjects (447 randomised to lixisenatide) were ≥65 years of age and 103 subjects (57 randomised to lixisenatide) were ≥75 years of age.

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

• Glycemic 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	Placebo	Lixisenatide 20 mcg		Placebo
			Morning	Evening	
	(N= 160)	(N= 159)	(N= 255)	(N= 255)	(N= 170)
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 hypoglycemia 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 hypoglycemia was reported in 3.4% of the lixisenatide patients compared to 1.2% in the placebo group.

Add-on combination therapy with a basal insulin

Lyxumia given with a basal insulin alone, or with a combination of a basal insulin and metformin, or a combination of a basal insulin and a sulphonylurea resulted in statistically significant reductions in

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

Table 4: Placebo-controlled studies in combination with a basal insulin (24-week results)

	Basal insulin as background therapy Alone or in combination with metformin		Basal insulin as background therapy Alone or in combination with a sulphonylurea *	
	Lixisenatide 20 mcg (N= 327)	Placebo (N= 166)	Lixisenatide 20 mcg (N= 154)	Placebo (N= 157)
Mean HbA_{1c} (%)				
Baseline	8.39	8.38	8.53	8.53
LS mean change from baseline	-0.74	-0.38	-0.77	0.11
Patients (%) achieving HbA_{1c} <7.0%	28.3	12.0	35.6	5.2
Mean duration of treatment with basal insulin at baseline (years)	3.06	3.2	2.94	3.01
Mean change in basal insulin dose (U)				
Baseline	53.62	57.65	24.87	24.11
LS mean change from baseline	-5.62	-1.93	-1.39	-0.11
Mean body weight (kg)				
Baseline	87.39	89.11	65.99	65.60
LS mean change from baseline	-1.80	-0.52	-0.38	0.06

*performed in Asian population

A clinical study was conducted in insulin-naive patients insufficiently controlled on oral antidiabetic agents. This study consisted of a 12-week run-in period with introduction and titration of insulin glargine and of a 24-week treatment period during which patients receive either lixisenatide or placebo in combination with insulin glargine and metformin with or without thiazolidinediones. Insulin glargine was continuously titrated during this period.

During the 12-week run-in period, addition and titration of insulin glargine resulted approximately in an HbA_{1c} decrease of 1%. The addition of lixisenatide led to a significantly greater HbA_{1c} decrease of 0.71% in the lixisenatide group compared to 0.40% in the placebo group. At the end of the 24-week treatment period, 56.3% of the lixisenatide patients achieved an HbA_{1c} less than 7 % compared to 38.5% in the placebo group.

During the 24-week treatment period, 22.4% lixisenatide patients reported at least one symptomatic hypoglycemic event compared to 13.5% in the placebo group. The incidence of hypoglycemia was mainly increased in the lixisenatide group during the first 6 weeks of treatment and thereafter, was similar to the placebo group.

- 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.

A meta-analysis of all independently adjudicated cardiovascular events (CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure and coronary revascularization procedure) from 8 phase III placebo-controlled studies which included 2673 type 2 diabetes patients treated with lixisenatide and 1448 patients treated with placebo showed a hazard ratio of 1.03 (95% confidence interval 0.64, 1.66) for lixisenatide versus placebo. The number of events in the clinical studies was low (1.9% in lixisenatide treated patients and 1.8% in placebo treated patients), precluding firm conclusions. The incidence of the individual CV events (lixisenatide vs placebo) was: CV death (0.3% vs 0.3%), non-fatal myocardial infarction (0.4% vs 0.4%), non-fatal stroke (0.7% vs 0.4%), hospitalization for unstable angina (zero vs 0.1%), hospitalization for heart failure (0.1% vs zero), and coronary revascularization procedure (0.7% vs 1.0%).

Pediatric population

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

There were no relevant differences in mean C_{max} and AUC of lixisenatide between subjects with normal renal function and subjects with mild impaired renal function (creatinine clearance calculated by the Cockcroft-Gault formula 50-80 ml/min). In subjects with moderate renal impairment (creatinine clearance 30-50 ml/min) AUC was increased by 24% and in subjects with severe renal impairment

(creatinine clearance 15-30 ml/min) AUC was increased by 46%.

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

Animal studies did not indicate direct harmful effects with respect to male and female fertility in rats.

Reversible testicular and epididymal lesions were seen in dogs treated with lixisenatide. No related effect on spermatogenesis was seen in healthy men.

In embryo-foetal development studies, malformations, growth retardation, ossification retardation and skeletal effects were observed in rats at all doses (5-fold exposure ratio compared to human exposure) and in rabbits at high doses (32-fold exposure ratio compared to human exposure) of lixisenatide. In both species, there was a slight maternal toxicity consisting of low food consumption and reduced body weight. Neonatal growth was reduced in male rats exposed to high doses of

lixisenatide during late gestation and lactation, with a slightly increased pup mortality observed.

6. Pharmaceutical particulars

6.1 List of excipients

Glycerol 85%

Sodium acetate trihydrate

Methionine

Metacresol

Hydrochloric acid (for pH adjustment)

Sodium hydroxide solution (for pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

After first use : 14 days

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store away from the freezer compartment.

After first use

Store below 30°C. Do not freeze.

Do not store with attached needle. 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 product side and polyisoprene on the outside). Each cartridge is assembled into a disposable pen.

Lyxumia 10 mcg

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

Pack containing 1 green pre-filled pen.

Lyxumia 20 mcg

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. MANUFACTURER:

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.

LICENSE HOLDER: sanofi-aventis Israel Ltd., P.O.B 8090, Netanya 4250499.

Registration Numbers:

LYXUMIA 10 MCG 1520633886

LYXUMIA 20 MCG 1520733893