Lixisenatide

▼Lyxumia® in type 2 Diabetes Mellitus

One more, but not getting ahead

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DRUG ASSESSMENT REPORT
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ABSTRACT

There are no clinical trials on the impact on mortality and the micro and macrovascular complications of diabetes.

It has only shown greater efficacy in the reduction of HbA_{1c} (difference *vs* placebo between -0.32% and -0.74%).

Long-term safety remains unknown (thyroid gland related, cardiovascular adverse effects and pancreatitis)

There are no advantages in efficacy, safety, posology or cost *vs* either the antidiabetic agents currently available or other GLP-1 agonists.

Indications[1]

Lixisenatide 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.

The drug is reimbursed by Spain's National Health System only for adult type 2 diabetes patients who are overweight (BMI> 30 kg/m^2) in combination therapy with diet, and exercise and with no adequate glycaemic control.

Mechanism of action and pharmacokinetics[1,2]

This GLP-1 analogue binds to GLP-1 receptors of beta cells in the pancreas stimulating the secretion of insulin when glycaemia levels increase, but not during normoglycaemia, and thus reduces the risk of hypoglycaemia. In addition, it suppresses the secretion of glucagon and slows down gastric emptying reducing the rate of absorption.

Peak plasma concentrations occur between 1-3.5 h. There are no clinically relevant differences in absorption when administered at the abdomen, thigh or at the upper arm. Plasma protein binding reaches 55%. The drug is eliminated through glomerular filtrate, tubular reabsorption and posterior metabolic degradation. The elimination half life is approximately 3 h.

Posology and administration[1]

Administration: subcutaneous in the thigh, abdomen or upper area of the arm.
Initial dose: 10 µg daily for 14 days. Maintenence: from the 15th day, 20 µg daily.
Conservation: between 2 and 8ºC before use, and below 30ºC after the first use (maximum 14 days).
It should be administered one hour before the first meal of the day or dinner. When a dose is ommited or forgotten, it should be administered one hour before the next meal.

Clinical efficacy

The effects of lixisenatide on morbidity and mortality are unknown. There are no comparative studies of lixisenatide with other elective hypoglycaemic agents: metformin +/- sulphonylureas +/- insulin.

Lixisenatide was more effective than placebo in the reduction of HbA1c after 24 weeks (difference vs placebo between -0.32% and -0.74%). The average weight reduction was approximately 1kg. In an open trial with exenatide as add-on therapy to metformin, the average reduction in HbA1c after 24 weeks (primary endpoint) was -0.79% for lixisenatide and 0.96% for exenatide (difference between groups, 0.17%; 95%CI, 0.033 to 0.297). Lixisenatide did not clearly demonstrate non inferiority and produced lower reductions in weight compared to exenatide, with a difference between treatments of approximately 1 kg.[7]

No additional advantages with respect to currently available antidiabetic agents

Safety

Adverse reactions[1]

The adverse effects are similar to those in other GLP-1 agonists. The most frequent adverse effects were nausea (26%), vomiting (10.5%) and diarrhoea (8.3%),[2] the majority mild and transitory. Hypoglycaemia has also been reported after concomitant use with sulphonylureas and/or basal insulin. Lixisenatide presented a lower incidence of nausea and symptomatic hypoglycaemia and a higher incidence of local reactions after administration when compared to exenatide.[7]

A transitory increase in heart rate after 20 µg lixisenatide has been observed, and heart arrhythmia, has been reported, particularly tachyarrhythmia (0.8% vs <0.1%) and palpitations (1.5% *vs* 0.8%) in comparison to placebo.

Contraindications[1]

Hypersensitivity to the main substance or any of its excipients.

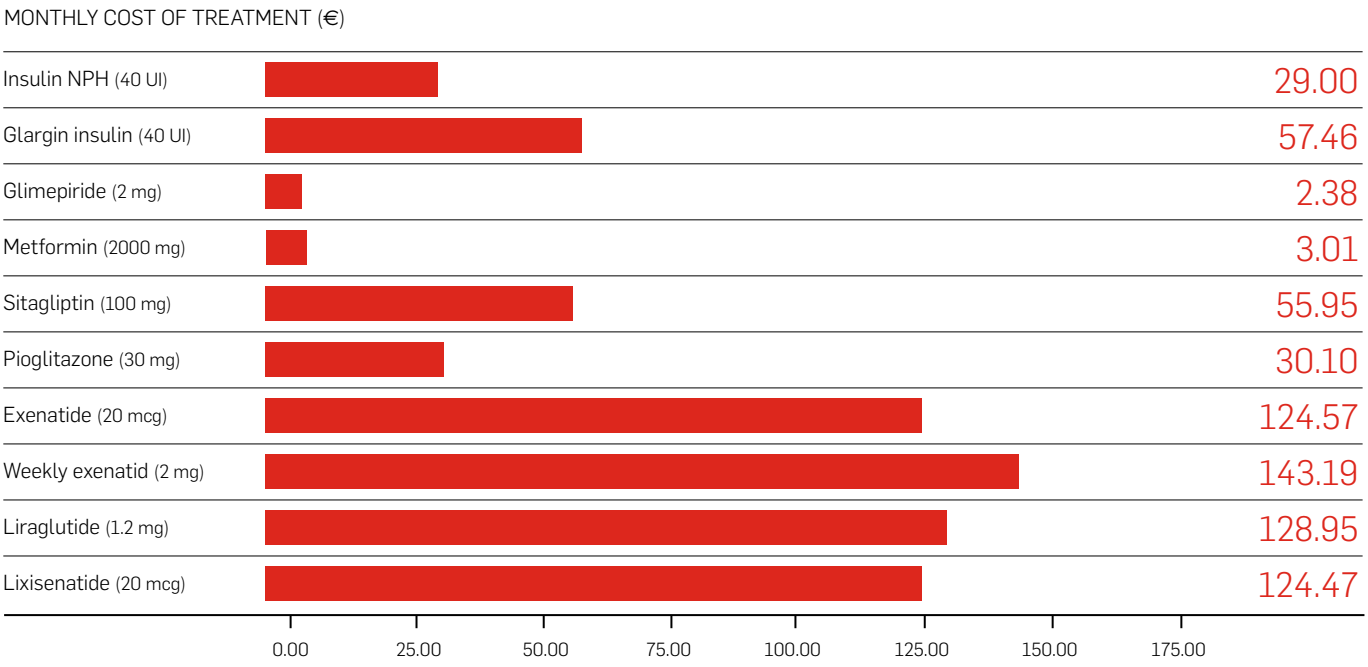
Warnings and precautions[1]

· Do not employ in type 1 diabetes or in diabetic ketoacidosis
· In cases of suspicion of pancretitis, treatment should be discontinued, and if confirmed, treatment should not be reintroduced. Take precaution in cases of history of pancreatitis.
· It is not recommended in cases of severe gastrointestinal disease.
· In cases of hypoglycaemia, reduce the dose of sulphonylureas or basal insulin. It should not

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



be administered in combination with basal insulin and a sulphonylurea.
· There are no studies on lixisenatide and dipeptidil peptidase 4 inhibitors (DPP-4)
· There is limited experience in patients with congestive heart failure.
· Precaution should be taken to avoid dehydration.
· This product contains metacresol as an excipient which can provoke allergic reactions.

Use in special situations[1]

Patients ≥ 75 years: although the product information leaflet does not indicate age-related dose adjustments, the clinical experience is still very limited (n=56). **Renal impairment.** If *moderate*, (Cr Cl = 30-50 mL/min), employ with precaution; *severe* (15-30 mL/min) and *terminal*, do not use. **Patients < 18 years:** the safety profile and efficacy has not been established yet. **Women in fertility age:** not recommended. **Pregnancy:** it should not be employed and should be interrupted in women who become pregnant or show desire. **Lactation:** not recommeded.

Interactions[1]

Precaution is recommended at treatment onset in patients under medications presenting rapid gastrointestinal absorption, requiring monitoring or with a narrow therapeutic range. Intake of the drug should be separated from food ingestion.

Gastro-resistant formulations and drugs dependent on threshold concentrations for efficacy like antibiotics should be administered 1 h before or 4 h after lixisenatide.

EMA Risk Management Plan[1]

Acute pancreatitis and/or pancreatic cancer, the development of antibodies, cardiovascular effects and the development of medular thyroid cancer are included in the EMA's risk plan to be studied in post-authorisation studies.[2]

Place in therapeutics

When monotherapy under metformin is ineffective, the clinical practice guidelines recommend the combination of metformin with a sulphonylurea. Glitazones (pioglitazone) or DPP-4 inhibitors can be associated with metformin or a sulphonylurea in double therapy when there is a contraindication or intolerance to any of them, or in patients with a particular risk profile (hypoglycaemia, overweight).[12-15]

When double therapy is ineffective a third antidiabetic agent is recommended, preferably insulin,[12-15] except if insulinization problems.

Taking into account the lack of data on efficacy in morbimortality, and long-term safety, GLP-1 agonists remain an option for triple therapy, substituting insulin in obese patients (BMI>30 kg/m^2) if there are serious problems with administering insulin or when there is a lack of efficacy or intolerance to previous treatments.[13-15] Treatment should be evaluated after 6 months and continued only if the reduction of HbA1c is at least by 1%, and weight loss by 3% with respect to baseline values.[14-15]

With regard to comparative efficacy with other GLP-1 agonists (exenatide and liraglutide), lixisenatide has been compared to exenatide[7] as add-on therapy to metformin. Lixisenatide has not shown a clear non-inferiority in the reduction of HbA1c or body weight compared to exenatide.[2]

The safety profile appears to be similar to that of the rest of GLP-1 agonists, although with a lower incidence of nausea and hypoglycaemia than exenatide.

Presentations

Lyxumia® (Sanofi-Aventis) 10 µg injectable solution, 14 doses (62.29 €); 20 µg injectable solution, 28 doses (124.57 €).

References

A complete report on lixisenatide can be found at: http://www.bit.navarra.es

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