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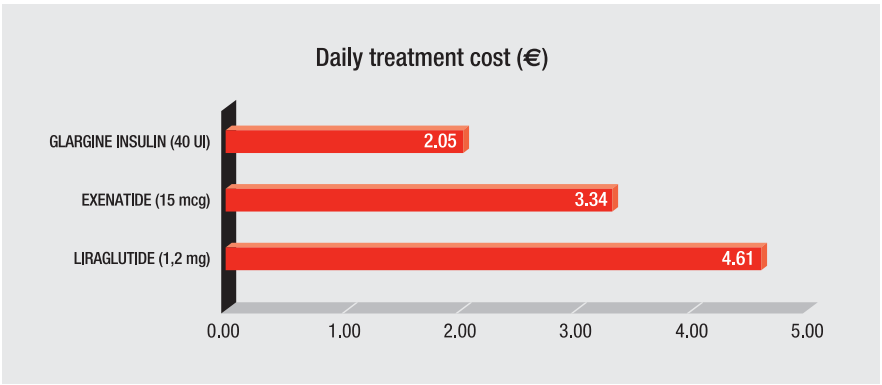
Liraglutide (Victoza®) in type 2 diabetes

Similar to exenatide



Another new arrival with no data on morbimortality

- The efficacy of liraglutide is similar to glimepiride and slightly higher than glargine and exenatide, although the clinical relevante is scarce.
- It produces weight loss comparable to exenatide, higher at the start of treatment and in patients with a high body mass index.
- Withdrawals due to adverse effects and the safety profile is similar to exenatide. The incidence of hypoglycemia is low, and increases when combined with suphonylureas.
- There is uncertainty with regard to the cardiovascular safety profile, its action on thyroid gland, pancreatitis and immunogenicity. There is no information available on long-term safety of the drug.
- There is no information on the efficacy with regard to diabetes complications and mortality.

Therapeutic indications[1,2]

Liraglutide is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, in combination with:
· Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.
· Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

It requires special authorization and can only be indicated in patients with a BMI ≥ 30 Kg/m^2.

Mechanism of action and pharmacokinetics[1]

This GLP-1 (glucagon like peptide-1) analogue increases the secretion of insulin and reduces that of glucagon, in a glucose dependent manner. It delays stomach voiding and produces a sensation of satiety that mildly reduces appetite[1,2]. It presents a C_{max} = 8-12 h, bioavialbility = 55%, plasma protein binding = 98% and a half life = 13 h. The elimination pathway is not clearly known.

Posology and method of administration[1]

The initial dose is 0.6 mg daily. After at least one week the dose can be increased to 1.2 mg daily. Given the response and after at least one week, an increase upto 1.8 mg daily can be reached[1,2]. Administration is subcutaneous, once daily, independent of meal times and preferably at the same time every day.

In combination with metformin or alone, or with a glitazone, no dose adjustments are needed for any of the agents. However, if a sulphonylurea is added (alone or with metformin) then a reduction in the dose of the sulphonylurea should be considered, given the risk of hypoglycaemia[1,2].

Clinical efficacy

The LEAD program (*Liraglutide Effect and Action in Diabetes)* represents 6 trials, one of which is in monotherapy LEAD-3, (indication not authorised[10]). There is also another open designed study published[16]. In total, more than 4000 diabetes patients have been treated with liraglutide in monotherapy or in combination, (18-80 years, with a BMI ≤ 40 kg/m^2). The dura-

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.

tion of these studies was 26 weeks[11-16]. The primary endpoint was a reduction in HbA_{1C}. With the exception of LEAD-4[13] (compared to placebo), the trials were non-inferiority studies. None of the studies included variables evaluating morbidity or mortality[2].

Liraglutide double therapy

LEAD-1 compared liraglutide to rosiglitazone. The latter was withdrawn in the European market due to cardiovascular problems[9,18]. LEAD-2 compared liraglutide (0.6, 1.2 and 1.8 mg daily) with glimepiride (4 mg daily) associated with metformin (2 g daily). The efficacy was similar (reduction of HbA_{1C} = -1%[12]).

An open study evaluated the efficacy and safety of liraglutide (1.2 and 1.8 mg daily) compared to sitagliptine (100 mg daily), combined with metfomrin (≥ 1,5 g daily)[16]. The reduction in HbA_{1C} was greater with metformin+liraglutide (-1.5%) than with metformin+sitagliptine (-0.9%). Difference =0.60% (95%CI = - 0.77 to - 0.43).

Liraglutide in triple therapy

LEAD-5 compared liraglutide (1.8 mg daily) with glargine insulin (100 U/mL) associated with metformin (2 g daily) and glimepiride (4 mg daily). The reduction in HbA_{1C} was statistically higher with liraglutide (-1.3%) than with glargine insulin (-1.1%) although the clinical relevance was scarce[14]. Treatment with glargine insulin was not blinded.

Liraglutida compared to exenatide (double and triple therapy)

LEAD-6 (open design) compared liraglutide (1.8 mg daily) with exenatide (10 mcg twice daily) combined with metfomin and/or a sulphonylurea[15]. The reduction in HbA_{1C} was slightly higher with liraglutide (-1.1%) than with exenatide (-0.8%), but of scarce clinical relevance. Difference = -0.33 (95%CI = -0.47 to – 0.18). Liraglutide produces weight loss, which is greater at the start of treatment and in patients with a high BMI (BMI ≥ 25 Kg/m^2) [2,3].

Safety and precautions for use

Adverse reactions

The adverse reactions were mild to moderate, dose dependent and temporary, appearing especially at the beginning of treatment[2,18,20]. The most frequent (10-40%) were gastrointestinal disorders (nausea, vomiting and diarrhoea) and in lesser proportion (3-6%) constipation, abdominal pain and dyspepsia[2,17,18,20-23].

The information on long-term safety of liraglutide is scarce[17,21]. The risk management plan of the European Medicines Agency (EMA) recommends an extension of the research on cardiovascular risk, neoplasm, thyroid disorders, pancreatitis, immunogenicity and on its employement in cases of renal impairment or liver alterations[2,18]. Withdrawals due to adverse effects were higher with liraglutide (2.1-15.2%) when compared to other agents[2,17,20], except for exenatide (13.4%)[15]. The incidence of severe adverse reactions was lower in the case of liraglutide compared to other antidiabetic agents, but higher than with exenatide[15,20,21]. In the total of adverse reactions, there were no significant differences between liraglutide and exenatide (74 and 78.9% respectively)[15].

Contraindications and precautions[1]

Do not employ this agent in type 1 diabetes or in cases of diabetic ketoacidosis. It is not recommended in cases of inflammatory bowel disease or diabetic gastroparesia. Patients should be notified of symptoms such as intense abdominal pain, persistent nausea and vomiting, given the potential risk of pancreatitis and treatement should be discontinued in case of any suspiscion[1,18].

Notifications have been received of adverse reactions affecting the thyroid gland, which includes calcitonin increments in blood, goitre, and thyroid neoplasm especially in patients with pre-existing thyroid disease.

When combined with sulphonylureas there is a higher risk of hypoglycaemia. Notifications of signs and symptoms of dehydration which include alterations in renal function. Patients should be warned of the risk of dehydration related to the undesirable gastrointestinal effects and should take precautions to avoid fluid loss.

Interactions[1]

Liraglutide is not metabolised via the P450 cytochrome[1,21]. Like exenatide, gastric voiding is delayed, which could alter the absorption of other drugs[1,21,22].

Special situations

Pregnancy and lactation: not recommended. **Elderly:** no dose adjustments are necessary in patients over 65 years, although experience is limited in those patients over 75 years. **Renal impairment:** it should not be employed in moderate (Cr Cl = 30-50 mL/min) or severe renal impairment (Cr Cl < 30 mL/min). **Patients under 18 years:** it should not be used. **It should not be employed** in patients with liver failure, congestive heart failure, inflammatory bowel disease and diabetic gastroparesia.

Place in therapeutics

Liraglutide is indicated in combined treatment with metformin or sulphonylurea and in triple therapy with metformin and sulphonylurea/thiazolidinedione, in adults with type 2 diabetes, who do not achieve adequate control. In order to be financed, this agent should be employed in patients with a BMI ≥ 30 Kg/m^2.

Its efficacy in double therapy is similar to glimepiride. In triple therapy and when compared to exenatide it is statistically slightly superior, although this is of scarce clinical relevance. The safety profile is similar to exenatide. The risk management plan issued by the EMA makes note of cardiovascular effects, thyroid disorders, (including neoplasm), pancreatitis and immunogencity. The FDA has just released a warning regarding thyroid-related disorders. The drugs long-term safety is not established as yet. Withdrawals due to undesirable effects were superior to the other comparators and were similar to exenatide. The incidence of hypoglycaemia is relatively low and increases when combined with a sulphonylurea. There are no long-term comparative studies, evaluating variables such as morbidity and mortality, quality of life of patients and the evolution of the disease.

Liraglutide produces weight loss (greater at the start of treatment and in patients with high BMI), at the expense of an unknown long-term safety profile. The difference with exenatide is the single dose administration, independent of meal times.

Combined treatment with GLP-1 analogues could represent an alternative in type 2 diabetes patients who need to lose weight. The NICE guidelines point out that treatment should be continued only if a favourable response is observed after 6 months, measured by a reduction of ≥ 1% in HbA_{1C}, and a weight loss of ≥ 3% when employing triple therapy[3].

The current evidence does not show that liraglutide presents therapeutic advantages over the other antidiabetic agents: no benefits have been shown with regard to efficacy or safety when compared to metformin+sulphonylurea (the gold standard in double therapy) or when compared to the possible alternatives in triple therapy.

Presentations

Victoza® (Novo Nordisk A/S) injectable solution (6 mg/mL) for injection in pre-filled pen (3 mL). Price: 138.16 €. Prescription medicine only, requiring additional special approval

References

A complete report on liraglutide is available at: http://www.dtb.navarra.es

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