Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS006
Liraglutide [Victoza®]	March 2019

VERDICT

Coventry & Warwickshire APC recommends that liraglutide (Victoza®) is used in line with current NICE NG28 on the management of Type 2 diabetes within its licensed indications. *Prescribers should refer to the APC's GLP-1 drugs comparison chart (DCC002) for information on the alternatives available including data on safety and cost*

Specialist Drugs Status: Specialist Advised (SA)

SUMMARY NOTES

Indication: Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue licensed for the treatment of type 2 diabetes[1].

Liraglutide can be used:

as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications.

in combination with oral glucose-lowering medicinal products and/or insulin when these, together with diet and exercise, do not provide adequate glycaemic control. Liraglutide can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.

Liraglutide can be added to existing sulfonylurea or to a combination of metformin and sulfonylurea therapy or a insulin. When liraglutide is added to sulfonylurea therapy or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia[1].

Presentation: It is administered once daily by subcutaneous injection

Dose: 0.6 mg daily increased to 1.2 mg after at least one week. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week, the dose can be increased to 1.8 mg to further improve glycaemic control[1].

Cost of 30 days treatment[2]

Liraglutide 1.2 mg daily	£78.48
Dulaglutide 0.75 mg (or 1.5 mg) weekly	£97.45
Exenatide 2 mg prolonged release once weekly	£78.60
Exenatide 5 or 10 micrograms twice daily	£68.24
Lixisenatide 20 micrograms daily	£57.93

Storage: Before use: Store in a refrigerator (2-8ºc) – In use: store below 30ºc or in a refrigerator away from freezer compartment.

DRUG PROFILE

Efficacy and safety was assessed in the LEAD trial (Liraglutide effect and Action in Diabetes) where liraglutide reduced mean HbA1c by 0.8 - 1.5% compared to placebo or other active comparators in various combinations (including rosiglitazone, glimepiride, insulin glargine or exenatide). The LEAD 6 study compared Liraglutide 1.8 mg daily with exenatide 10 micrograms twice daily in combination with metformin, a sulphonylurea or both. Liraglutide was more effective at reducing HbA1c from baseline to week 26 (-1.12% liraglutide vs -0.79% exenatide). In both treatment groups, HbA1c reached its lowest point at 12 weeks and then started to increase, so it is not known if this effect is sustained[3].

Cardiovascular outcomes were determined in a long term multicentre, double-blind, placebo-controlled trial at 410 sites in 32 countries. 9430 patients with type 2 diabetes and high cardiovascular risk were randomly assigned to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for non-inferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007).

DRUG PROFILE cont'd

The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure were non-significantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was non-significantly lower in the liraglutide group than in the placebo group[4].

Liraglutide promotes a similar weight loss to exenatide (liraglutide -3.24kg vs exenatide 2.87kg) which is similar to exenatide[3].

Adverse effects

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of the therapy, these gastrointestinal adverse reactions may occur more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and nasopharyngitis were also common. Furthermore, hypoglycaemia was common, and very common when liraglutide is used in combination with a sulfonylurea. Major hypoglycaemia has primarily been observed when combined with a sulfonylurea[1].

Cautions

Elderly patients (>65 years old): No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited[1].

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 and liraglutide cannot currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease[1] .

Hepatic impairment: No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Liraglutide is not recommended for use in patients with severe hepatic impairment[1].

Acute pancreatitis: Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis[1].

Thyroid disease: Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease and liraglutide should therefore be used with caution[1].

Dehydration: Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in patients treated with liraglutide. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion[1].

CURRENT PLACE IN THERAPY

NICE Guidance NG28 recommends that if triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-) mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity-related comorbidities

Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months)[5].

The guideline also recommends to only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant led multidisciplinary team[5].

Summary

- Liraglutide was more effective at reducing HbA1c versus exenatide at week 26 [1].
- Liraglutide promotes weight loss (mean body weight loss of 3kg) which is similar to exenatide[1]. Liraglutide as Saxenda, is now licensed for weight loss (with preset criteria) and has a different dose range[6].
- A long-term study has demonstrated that the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.[4]

References

1. Summary of product characteristics (Victoza®). Last updated 7/10/16. Available via www.medicines.org.uk on 5/7/17
2. Dictionary of medicines and Devices June 2017. Accessed via https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff on 20/6/17
3. Buse J, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26 week randomised, parallel group, multi-national open label trial (LEAD-6) 2009. Lancet 374: 39-47,2009. Available at https://www.ncbi.nlm.nih.gov/pubmed/19515413 accessed 5/7/17
4. Marso, S, Daniels G, Brown-Frandsen K et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes 2016. N Engl J Med 2016; 375:311-322. Available at http://www.nejm.org/doi/full/10.1056/NEJMoa1603827#t=article accessed 17/6/17
5. National Institute for Health and Clinical Excellence NG 28 Type 2 diabetes: the management of type 2 diabetes. December 2015. Available at https://www.nice.org.uk/guidance/ng28 on 20/6/17
6. Summary of product characteristics (Saxenda®), Date of revision of text 16/1/2017 Accessed via www.medicines.org.uk on 5/7/17.