Cost-effectiveness of liraglutide (Victoza®) for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

The NCPE has issued a recommendation regarding the cost-effectiveness of liraglutide (Victoza®). Following assessment of the applicant's submission, the NCPE recommends that liraglutide (Victoza®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Novo Nordisk Ltd) economic dossier on the cost effectiveness of liraglutide (Victoza®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2019**

Summary

Liraglutide (Victoza®) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA), which was first launched in Ireland in 2009. The recommended starting dose of Victoza® is 0.6mg once daily. After at least one week, the dose should be increased to 1.2mg once daily. Some patients may benefit from an increase in dose, from 1.2mg to 1.8mg once daily, to further improve glycaemic control.

In 2009, at the time of initial launch, a formal health technology assessment of liraglutide was not conducted as evidence suggested that it would be prescribed at a dose of 1.2mg once daily for the majority of patients. However, in recent years, the number of patients being prescribed liraglutide at the higher dose has increased to the point that a similar rate of prescribing of both doses is now being observed. This prompted that a retrospective health technology assessment of liraglutide be conducted.

In September 2017, Novo Nordisk Ltd submitted a dossier to support the comparative clinical effectiveness and cost-effectiveness of liraglutide (Victoza®) for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise either:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; or
- in addition to other medicinal products for the treatment of type 2 diabetes

In their submission, Novo Nordisk Ltd presented exenatide as the most relevant comparator to liraglutide. However, the NCPE considered that the more appropriate focus should be to assess the incremental cost and clinical benefits of prescribing liragutide at the higher dose of 1.8mg once daily compared to 1.2mg once daily. This formed the NCPE preferred base case. Additional comparators were other GLP-1 RAs, including exenatide and dulaglutide.

1. Comparative effectiveness of liraglutide

Clinical evidence to support liraglutide, in the management of patients with type 2 diabetes, existed in the form of the LEAD-programme. This programme consisted of six phase III, randomised, controlled, parallel-group trials. The majority were multi-national, multi-centre trials with the exception of LEAD-3 and LEAD-4, which were both multi-centre trials conducted across two countries. All six trials followed similar methodologies with the primary efficacy endpoint being a measure of the change in Hb_{A1C}.

In LEAD-1 and LEAD-2, three treatment doses of liraglutide once daily were investigated: 0.6mg, 1.2mg and 1.8mg. LEAD-3 and LEAD-4 investigated the two proposed therapeutic doses of 1.2mg and 1.8mg. LEAD-5 and LEAD-6 investigated only liraglutide 1.8mg. Comparators varied across all six clinical trials. In LEAD-1, LEAD-2, LEAD-4 and LEAD-5, liraglutide demonstrated superiority over placebo in reducing Hb_{A1C} from baseline. In LEAD-3, liraglutide 1.2mg and 1.8mg both demonstrated significantly greater reductions in Hb_{A1C} from baseline compared with glimepiride 8mg once daily. In LEAD-6, liraglutide 1.8mg once daily demonstrated superior efficacy to exenatide 10mcg twice daily in reducing Hb_{A1C} from baseline.

Several limitations associated with the clinical evidence were identified. Firstly, the trials were of short duration, ranging from 26 to 52 weeks. This limitation has been addressed, in part, following completion of the five-year LEADER trial which provided long-term cardiovascular outcomes of liraglutide compared to placebo. A second limitation relates to the dosing of certain comparators in some of the trials. For example, in LEAD-1, one of the comparators, rosiglitazone, is prescribed at a dose of 4mg once daily. In Europe, rosiglitazone may be prescribed at a maximum dose of 8mg once daily. Also, evidence suggests that the effectiveness of rosiglitazone is expected to be more pronounced after one year, whereas the duration of the LEAD-1 trial was 26 weeks. These factors may have led to an underestimation of the efficacy profile of rosiglitazone. In LEAD-3 the relevant comparator, glimepiride, was prescribed at a dose of 8mg once daily. However, in Europe recommended doses would be in the region of 2mg to 4mg once daily, with a maximum of 6mg once daily. The comparator dose was, therefore, considered to be high and may have contributed to a greater number of hypoglycaemic events in the glimepiride group. This may

subsequently have resulted in an overestimation of the safety of liraglutide for this particular trial.

2. Safety of liraglutide

Dose related gastrointestinal disturbances, including nausea, vomiting and diarrhoea, were the most frequently reported adverse effects associated with liraglutide (Victoza®) throughout the course of the six LEAD trials, and the LEADER trial. Headache and nasopharyngitis were also commonly reported as was hypoglycaemia, especially when prescribed concomitantly with a sulphonylurea.

3. Cost effectiveness of liraglutide 1.8mg

Methods

A cost-utility analysis comparing liraglutide 1.8mg with exenatide, was presented by the applicant in their base case analysis. The Review group considered there to be other comparators of interest for this HTA. The Review group requested additional cost effectiveness analysis, where liraglutide 1.8mg was compared with liraglutide 1.2mg and with dulaglutide 1.5mg.

The CORE Diabetes Model (CDM) was used, which is an individual patient stochastic simulation model, which uses Markov Chain Monte Carlo methods. This model choice meant that the workings of the model could not be interrogated by the Review Group, only the inputs presented. The CDM includes 17 interdependent sub-models that are included to simulate the complications of diabetes. Each sub-model consists of a series of states, to simulate that particular complication associated with diabetes. The Health Service Executive (HSE) perspective and a lifetime (40 years) time horizon were used. The main model has a one-year cycle length; the foot ulcer sub-model has a cycle length of one month; the hypoglycaemia sub-model has a cycle length of three months.

The source of treatment effects for both the intervention and the comparator, when liraglutide 1.8mg was compared with exenatide 10mcg was the LEAD-6 trial. For liraglutide 1.8mg compared with liraglutide 1.2mg and dulaglutide 1.5mg, the treatment effects were

calculated using findings from a meta-analysis. Within the CDM, the UK Prospective Diabetes Study Outcomes model (UKPDS 68) was used to calculate the risk of cardiovascular events. The equations derived from UKPDS 68 were applied to calculate risks of MI, stroke, angina and heart failure.

The majority of the utility values were derived from a published systematic literature review of diabetes and its complications. The relevant utilities that were not collected in this study were derived from two additional studies. In the economic model, QALYs were calculated as a function of the states of diabetic complications that were reached in a given year of simulation. Any acute events, which were associated with a disutility, were also applied to that given year. When more than one diabetic complication was incurred by a patient, the lowest utility value was chosen.

There were some uncertainties associated with the utility values used. The studies from which the utilities are derived are four or more years old, and it is unclear how the studies were identified and selected. No details of any review being undertaken for health outcomes were presented by the applicant. Therefore, it is not clear if these are the most appropriate sources of utility values for this submission.

The cost categories included in the model were drug acquisition costs; administration costs; and the management costs relating to T2DM and its complications. The costs of background therapy, in addition to the intervention and comparators of interest, were not included in the analysis. Any dose reductions recommended due to background therapy were also not included. It is assumed that the level of dose reduction would be equivalent in both arms, since both arms have equivalent background therapy. It is not clear what effect the inclusion of the costs of background therapies would have on the results.

The applicant states that Irish costs were used where available. These were supplemented with UK costs and costs derived from a UK based systematic review, where necessary. Given that the costs included were not all based on Irish costs, a sensitivity analysis where the costs were increased/decreased by 20% was undertaken.

Results

The applicant conducted an incremental analysis comparing liraglutide 1.8mg to exenatide 10mcg, liraglutide 1.2mg and dulaglutide 1.5mg. The results of a deterministic analysis were presented for all comparisons. The results of a probabilistic analysis, using 1,000 iterations were presented for the comparisons with exenatide 10mcg and liraglutide 1.2mg only.

In the deterministic analysis of incremental cost per QALY (incremental cost-effectiveness ratio (ICER)), the ICER comparing liraglutide 1.8mg with exenatide 10mcg was €9,820/QALY. Liraglutide 1.8mg was associated with 0.087 greater QALYs at a greater cost of €858. In the probabilistic analysis, the ICER was €10,361/QALY. Liraglutide 1.8mg was associated with 0.08 greater QALYs at a greater cost of €857. The applicant states that, at a willingness to pay threshold of €45,000/QALY, liraglutide 1.8mg has a 97% probability of being cost-effective compared with exenatide 10mcg.

In the deterministic analysis comparing liraglutide 1.8mg with liraglutide 1.2mg, the ICER was €36,214/QALY. Liraglutide 1.8mg was associated with 0.023 greater QALYs at a greater cost of €844. In the probabilistic analysis, the ICER was €44,570/QALY. Liraglutide 1.8mg was associated with 0.019 greater QALYs at a greater cost of €856. The applicant states that, at a willingness to pay threshold of €45,000/QALY, liraglutide 1.8mg has a 50% probability of being cost-effective compared with liraglutide 1.2mg.

In the deterministic analysis comparing liraglutide 1.8mg with dulaglutide 1.5mg, the ICER was €117,402/QALY. Liraglutide 1.8mg was associated with 0.015 greater QALYs at a greater cost of €1,785. A probabilistic sensitivity analysis was not presented for liraglutide 1.8mg compared with dulaglutide 1.5mg.

The Review Group requested additional scenarios to be undertaken. Following the concerns about the two network meta-analyses (NMAs) presented as clinical evidence for the economic model, the RG requested the applicant to conduct additional sensitivity analyses around the HbA_{1c} values used. In these analyses, the upper and lower bounds of the analysis for the change in HbA_{1c} were derived across the three NMAs available. The ICERs for the comparison of liraglutide 1.8mg with liraglutide 1.2mg ranged from € 17,009/QALY to € 784,578/QALY for the lower and upper bounds of HbA1c respectively. The ICERs for the comparison of liraglutide 1.8mg with exenatide ranged from € 6,334/QALY to € 17,407/QALY for the lower and upper bounds of HbA1c respectively. The ICERs for the comparison of liraglutide 1.8mg with dulaglutide 1.5mg ranged from liraglutide

being dominated (more costly and less effective) to € 54,745/QALY for the lower and upper bounds of HbA1c respectively. This sensitivity analysis highlights the very large effect on the ICER for all comparisons, due to changes in the HbA_{1c} values.

4. Budget impact of liraglutide

Liraglutide is formulated as a 3ml pen containing 6mg/ml solution for injection. It is available as a 2-pen or 3-pen pack corresponding to doses of 1.2mg once daily and 1.8mg once daily, respectively. The list prices for the 2- and 3-pen packs are €98.39 and €147.10, respectively. The annual cost, per patient, to the HSE is €1,497 for those prescribed liraglutide 1.2mg once daily and €2,197 for those prescribed 1.8mg once daily. Based on current market share values, it is estimated that the cumulative five year gross budget impact for liraglutide 1.2mg once daily and liraglutide 1.8mg once daily, will be €22.1million and €35.2million, respectively. Total expenditure on liraglutide over the same period is estimated to be in excess of €57million. As liraglutide is currently available and reimbursed under the General Medical Services (GMS) scheme in Ireland, it is not anticipated that it will significantly displace other drugs. Therefore, the net budget impact is considered to be the same as the gross budget impact.

5. Patient submission

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

The NCPE assessment of liraglutide 1.8mg has demonstrated improvements in diabetes control over the comparative treatments. However, there were limitations in the clinical evidence used to inform the comparisons of liraglutide 1.8mg with liraglutide 1.2mg and with dulaglutide 1.5mg. The scenario analysis requested by the review group highlights the uncertainty that is incorporated into these cost-effectiveness analyses, due to the clinical evidence used. In addition, it is important to note that the model provided by the applicant was not an executable model and therefore could not be validated by the Review Group. Following assessment of the applicant's submission, the NCPE recommends that liraglutide (Victoza®) 1.8mg not be considered for reimbursement unless cost effectiveness can be

improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.