Cost-effectiveness of liraglutide 3mg (Saxenda®) as an adjunct to a reduced calorie diet and increased physical activity for weight management in adult patients with a body mass index of ≥35kg/m^2 with pre-diabetes and high risk of cardiovascular disease.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of liraglutide 3mg (Saxenda®). Following assessment of the applicant's submission, the NCPE recommends that liraglutide 3mg (Saxenda®) 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 NCPE to carry out an assessment of the Applicant's (Novo Nordisk Ltd) economic dossier on the cost effectiveness of liraglutide 3mg (Saxenda®). 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 **February 2021**

Summary

Liraglutide 3mg (Saxenda®) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA), which has combined effects on body weight and also on glycaemic control. The marketing authorisation for liraglutide 3mg was granted by the European Medicines Agency on 23 March 2015. The starting dose of liraglutide is 0.6mg once daily. The dose should be increased to 3mg once daily in increments of 0.6mg with at least one week intervals to improve gastro-intestinal tolerability. Treatment should be discontinued after 12 weeks on the 3mg per day dose if patients have not lost at least 5% of their initial body weight.

Liraglutide 3mg daily (Saxenda®) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of ≥30kg/m^2 (obese), or ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus [T2DM]), hypertension, dyslipidaemia, or obstructive sleep apnoea.

Novo Nordisk Ltd (the Applicant) presented an analysis to support clinical and cost effectiveness of liraglutide 3mg once daily compared to diet and exercise alone. In their submission (May 2020), the Applicant's analysis examined the use of liraglutide 3mg once daily in a sub-group of the full licensed population, i.e. in patients with an initial BMI ≥35kg/m^2 with prediabetes and high risk of cardiovascular disease who will be treated within specialist weight management centres. However, after consultation with clinical leads, the NCPE Review Group considered that a more appropriate analysis would have been to assess the clinical and cost effectiveness of liraglutide 3mg once daily as per the licensed indication. Since this was not presented, the NCPE appraised the analysis as presented by the Applicant, i.e. in a sub-group of the licensed population.

1. Comparative effectiveness of liraglutide 3mg

Clinical evidence supporting the efficacy of liraglutide 3mg once daily for marketing authorisation was derived from the SCALE development programme that included one phase II dose-finding trial (Trial 1807) and four confirmatory phase IIIa trials (Trials 1839, 1922, 3970, and 1923). Across the trials, 5,813 subjects were exposed to treatment: 3,872 to liraglutide and 1,941 to placebo. The Applicant's submission focusses on a post-hoc analysis from one trial: the SCALE obesity and prediabetes trial (Trial 1839). Trial 1839 was a randomised, double-blind placebo controlled, parallel group, multicentre, multinational trial in patients who were obese (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities. Study participants were randomised two to one to receive liraglutide 3mg (n=2,487) or placebo (n=1,244) once daily as an adjunct to diet and exercise and stratified according to prediabetes status at screening. The trial was conducted in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. The co-primary endpoints at week 56 of the trial were (i) mean change from baseline in body weight; (ii) proportion of patients losing 5% or greater of fasting body weight; and (iii) proportion of patients losing more than 10% of baseline fasting body weight all assessed in a hierarchical manner. Liraglutide 3mg once daily resulted in a 5.39% greater weight loss as compared with placebo at week 56 ($p<0.0001$). A statistically significantly greater proportion of patients treated with liraglutide 3mg (63.2%) lost at least 5% of baseline body weight at week 56 compared to those treated with placebo (27.1%). Trial 1839 continued up to week 172, where the degree of weight loss observed decreased over time. Pooled analysis of trials in the SCALE programme (n=5813), undertaken to support product registration, demonstrated that weight decline reached a plateau after approximately 40 weeks.

The Applicant's choice to focus on a post-hoc subgroup analysis is a concern as it means that their analyses is based on a smaller sample of only 35% of the whole trial population (n=800). An unplanned post hoc analysis is inappropriate to inform the benefit in this subgroup because it can be subject to bias introduced by the analysis.

2. Safety of liraglutide 3mg

The most frequent adverse events in Trial 1839 were nausea (41% for liraglutide 3mg versus 14% for placebo), nasopharyngitis (28% vs 27%), diarrhoea (26% vs 12%), constipation (20% vs 10%), vomiting (18% vs 5%), headache (18% vs 16%) and upper respiratory tract infection (17% vs 16%). Hypoglycaemia, decreased appetite, fatigue, dizziness, and gastroenteritis were also more commonly reported with liraglutide 3mg than with placebo.

3. Cost effectiveness of liraglutide 3mg

Methods

A de novo Markov cohort model was developed in MS Excel™ comprising of 18 health states. Liraglutide 3mg once daily plus diet and exercise was compared to a programme of diet and exercise alone. There were four potential health complications; T2DM, post-acute coronary syndrome, stroke, and cancer. The 18 health states consisted of normal glucose tolerance (1 state), prediabetes (1 state), each of the four complications separately (4 states), a combination of any two complications (6 states), a combination of any three complications (4 states), all four complications (1 state), and death (1 state). Osteoarthritis and obstructive sleep apnoea were also considered as complications in the model, but not as distinct health states.

The source of treatment effects for both the intervention and the comparator was the post-hoc analysis from Trial 1839. Transitions between health states were based on the estimation of T2DM status, cardiovascular events (primary and secondary) using risk models as well as death probabilities. Health state utility values were sourced from published literature. Costs included in the model were acquisition and administration costs of obesity treatment, pharmacy costs (blood pressure and T2DM medications), and costs of obesity-related complications.

Results

The Applicant conducted a cost-effectiveness analysis comparing liraglutide 3mg once daily vs diet and exercise alone.

In the deterministic analysis of incremental cost per QALY (incremental cost-effectiveness ratio [ICER]), the ICER comparing liraglutide 3mg daily with diet and exercise alone was €25,668 per QALY. Liraglutide 3mg was associated with 0.067 greater QALYs at a greater cost of €1,710.

The Review Group noted a number of uncertainties with the assumptions in the model that were likely to impact on the cost effectiveness of liraglutide 3mg, including liraglutide 3mg treatment duration, waning of liraglutide 3mg effectiveness as well as the proportion of non-responders. Incorporating these changes into the NCPE's adjusted base case resulted in an ICER of €63,199 per QALY. Liraglutide 3mg was associated with 0.058 greater QALYs at a greater cost of €3,638. At willingness-to-pay thresholds of €20,000 and €45,000 per QALY, the probability of liraglutide 3mg being cost effective compared with diet and exercise alone was 0%.

There were also a number of other changes which the Review Group requested but the Applicant declined to make (such as assessing cost effectiveness in the full licensed population). Scenario analyses conducted by the Review Group identified the patient population as a key driver in the model. This parameter had a significant impact on the ICER; using the full Trial 1839 population, (which included patients with a lower BMI and a proportion of patients who were normoglycaemic), resulted in an ICER of €115,424 per QALY. When Trial 1922 (which included only patients with a diagnosis of T2DM) is used to inform clinical benefit, the resultant ICER increased to €167,945 per QALY.

4. Budget impact of liraglutide 3mg

The Applicant estimated the gross drug budget impact on the basis of an annual drug price of €3,563.88 (including VAT 23%). The Applicant's analysis assumed that patients receive treatment for two years (specifically there is no discontinuation after the 12 week stopping rule) and after two years all patients stop treatment.

The Review Group received clinical opinion to validate certain assumptions used in the model. For the Review Group's base case it was assumed patients that patients would receive treatment for five years. The Review Group also aligned the rate of discontinuation with that used in the cost effectiveness model. The Applicant estimated the five-year cumulative gross drug budget impact to be €8 million. Applying the Review Group's assumptions the estimated five-year gross budget impact was €10.2 million.

As identified in the cost-effectiveness analyses, a key driver in the model related to the population used. The Review Group therefore performed an additional scenario analysis to explore uncertainty associated with the Applicant's proposed sub-population and attempted to quantify the budget impact associated with treating patients in the full licensed population within specialised weight management centres. This analysis results in a five-year cumulative gross drug budget impact of approximately €37million.

For the Applicant's proposed target population liraglutide 3mg is not displacing the use of any other medicine, therefore, the net budget impact estimates were considered equal to the gross budget impact estimates.

5. Patient submission

A patient organisation submission was received during the course of this assessment and this will be provided to the HSE. This submission will form part of the data that the HSE considers.

6. Conclusion

Clinical evidence for liraglutide 3mg once daily did demonstrate improvements in weight loss over diet and exercise alone. However, there were limitations in this clinical evidence which were used to inform the comparisons provided by the Applicant. The scenario analysis conducted by the Review Group highlights the uncertainty that is incorporated into these cost-effectiveness analyses.

Following assessment of the Applicant's submission, the NCPE recommends that liraglutide 3mg (Saxenda®) 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.