The cost-effectiveness of oral semaglutide (Rybelsus®) for the treatment of adult patients with type II diabetes mellitus

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of oral semaglutide (Rybelsus®) for the treatment of adult patients with type II diabetes mellitus. The NCPE recommends that oral semaglutide should not be considered for reimbursement unless cost-effectiveness can be improved relative to existing therapy. 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) economic dossier on the cost effectiveness of oral semaglutide for the treatment of adults with type II diabetes. 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.

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

Novo Nordisk submitted an economic dossier (18/11/2020) on the cost-effectiveness of oral semaglutide (Rybelsus®) for the treatment of adult patients with type II diabetes mellitus. Diabetes mellitus is a chronic progressive metabolic disease defined by the presence of hyperglycaemia. A fasting blood glucose ≥ 7.0 mmol/l or a random blood glucose ≥ 11.1 mmol/l is required to make the diagnosis. A 2 hour blood glucose ≥ 11.1 mmol/l during an oral glucose-tolerance test is also confirmatory. An elevated glycosylated haemoglobin (HbA1c) ≥ 6.5% or 48 mmol/mol can also be used for diagnostic purposes. Type II diabetes mellitus which accounts for up to 90% of diabetes cases is characterised by insulin resistance and inadequate secretion of insulin. Prolonged, suboptimal glycaemic control leads to an increased risk of macrovascular (e.g. myocardial infarction, stroke and heart failure) and microvascular (e.g. retinopathy, neuropathy and nephropathy) complications. Metformin is recommended as first line therapy for type II diabetes mellitus however many patients will require intensification of therapy over time with the addition of agents from other therapeutic groups including sulphonylureas, thiazolidinediones, dipeptidyl peptidase-4-inhibitors (DPP-4 inhibitors), sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors), glucagon-like peptide-1 receptor agonists (GLP-1-RA) or basal insulin.

Semaglutide (Rybelsus®) is the first oral GLP-1 receptor agonist which reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is elevated. Conversely, it diminishes insulin secretion without impairing glucagon release during hypoglycaemia. Semaglutide also delays gastric emptying in the early postprandial phase. It reduces body weight and body fat mass through reducing appetite. The mechanism of action of semaglutide is independent of the route of administration. The starting dose of oral semaglutide is 3mg once daily for one month. After one month the dose should be increased to a maintenance dose of 7mg once daily. After at least one month the dose can be increased again to a maintenance dose of 14mg once daily to further improve glycaemic control. The maximum recommended single daily dose of oral semaglutide is 14mg.

1. Comparative effectiveness

The submitted dossier outlined the PIONEER clinical development programme supporting the registration of oral semaglutide. This consisted of eight randomised controlled phase III trials. In seven trials the primary objective was the assessment of glycaemic efficacy and in the remaining trial the primary objective was the assessment of cardiovascular outcomes. The trials included 8,842 patients with type II diabetes (5,169 treated with oral semaglutide), including 1,165 patients with moderate renal impairment. Patients had an average age of 61 years (range 18 – 92 years) with 40% being ≥ 65 years of age and 8% ≥ 75 years of age. The efficacy of oral semaglutide was compared with placebo (in PIONEER studies 1,5,8) or active controls including sitagliptin (PIONEER 3&7), empagliflozin (PIONEER 2) and liraglutide (PIONEER 4). The Peptide Innovation for Early Diabetes Treatment 6 (PIONEER 6) was a pre-approval cardiovascular outcomes trial specifically designed to rule out an excess in cardiovascular risk with oral semaglutide among patients with type II diabetes. The study indicated that the cardiovascular risk profile of oral semaglutide was not inferior to that of placebo.

The main clinical evidence used to support the economic evaluation was derived from the PIONEER studies which compared oral semaglutide with active comparators including empagliflozin, sitagliptin and liraglutide. As there are no head-to-head trials comparing oral semaglutide with other GLP-1 receptor agonists which are relevant comparators the Applicant presented a network meta-analysis (NMA) based on studies identified in the systematic literature review. The NMA informed the economic evaluation of oral semaglutide versus once weekly subcutaneous semaglutide (Ozempic®) and dulaglutide.

2. Safety

In ten phase III trials some 5,707 patients were exposed to oral semaglutide alone or in combination with other glucose-lowering products. The duration of treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse reactions in clinical trials were gastrointestinal (GIT) disorders, including nausea (15%), diarrhoea (10%) and vomiting (7%). To reduce GIT adverse events treatment with oral semaglutide is initiated with a dose escalation schedule. Gastrointestinal adverse events lead to treatment discontinuation in

approximately 4% of patients.

Other common adverse events include hypoglycaemia when used with other oral diabetic products (particularly insulin and sulphonylureas), diabetic retinopathy complications including vitreous haemorrhage, diabetes related blindness, treatment with intravitreal agents and the requirement for retinal photocoagulation. Fatigue and raised amylase are also common. Less frequent adverse events include increased heart rate (a feature of GLP-1 receptor agonists), cholelithiasis, weight reduction and rarely acute pancreatitis. In the PIONEER 6 study there were no unexpected adverse events including no increase in malignant neoplasms (2.6% in the oral semaglutide group and 3% in the placebo group). This is of importance following the increased rate of pancreatic cancer observed in the liraglutide group in the LEADER trial.

3. Cost effectiveness

The IQVIA CORE diabetes model (CDM), version 9.0 was used to assess the cost-effectiveness of oral semaglutide versus relevant GLP-1 receptor agonists and the SGLT-2 inhibitor empagliflozin in this economic evaluation. The model is based on a series of inter-dependent sub-models that simulate non-specific mortality and the complications of diabetes including angina pectoris, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer and amputation. Each sub-model has a semi-Markov structure and uses time, state, time-in-state and diabetes type-dependent probabilities derived from the published literature. The CDM was used to estimate long-term clinical and economic outcomes. The base case analysis used the UK Prospective Diabetes Study (UKPDS) 68 risk equations to predict the incidence of first cardiovascular events and a sensitivity analysis was conducted using the UKPDS 82 risk equations. The base case analyses used a lifetime (60-year) time horizon to capture all relevant long-term complications and associated costs and to assess their impact on life expectancy and quality of life. The model considered mortality as a result of diabetes-related complications and background mortality based on Irish-specific life tables from the Central Statistics Office.

The modelling approach to treatment duration and parameter progression is an important consideration. Following the application of the treatment effects in the first year of analysis, HbA1c was modelled to follow the UKPDS progression equation and patients were assumed to receive oral semaglutide or comparator treatment until the HbA1c reached 7.5% (58.5 mmol/mol). At this stage, treatment with oral semaglutide or the comparator was discontinued and patients were assumed to intensify treatment to basal insulin, with the reduction in HbA1c based on an insulin-naïve population derived from the 'Core' multivariate equations. The HbA1c was subsequently modelled to follow the UKPDS progression equation for the remainder of patient lifetimes. Due to variations in the initial HbA1c reductions, patients were assumed to receive oral semaglutide or comparator treatment for different lengths of time. For the comparison of oral semaglutide 14mg daily versus empagliflozin 25mg daily, sitagliptin 100mg daily and liraglutide 1.8mg per day, population and treatment effectiveness data was obtained from the head-to-head clinical trials PIONEER 2, 3 and 4 respectively. The network meta-analysis was used to inform treatment effectiveness for the comparison of once daily oral semaglutide versus once weekly subcutaneous dulaglutide 1.5mg and semaglutide 1mg, as no head-to-head trials were available.

The long-term outcomes that were evaluated included life expectancy, quality adjusted life expectancy in addition to the cumulative incidence and time to onset of diabetes-related complications. In the economic model health outcomes were expressed as quality adjusted life years (QALYs). Utilities associated with diabetes and diabetes-related complications were taken from a systematic literature review with additional disutilities applied for treatment administration. Resource usage and costs considered in the model included drug acquisition costs, patient management costs and costs associated with the treatment of diabetic complications. Oral semaglutide drug acquisition cost applied in the model was for a pack size of 30 where the price to wholesaler was €102.28. The total cost per patient per annum was €1,347.88 (including wholesale mark-up and pharmacy fees). The analysis was from the perspective of the Health Service Executive (HSE) and a discount rate of 4% was applied in line with current guidelines.

The NCPE Review Group had a number of concerns in relation to the modelling approach

including (a) treatment discontinuation at years 2 and 3 for empagliflozin and oral semaglutide does not reflect current practice in Ireland where additional hypoglycaemic agents are added to current therapy as opposed to discontinuing treatment (b) discontinuing empagliflozin after 2 years is highly unlikely and ignores the long term benefits of this drug on cardiovascular outcomes such as CHD and heart failure in addition to the proven beneficial effects on renal function (c) differences in parameters such as BMI and systolic blood pressure which favoured oral semaglutide in the modelling exercise were not statistically significant in the PIONEER 2 trial using the treatment policy estimand approach (d) it is hard to justify the persistence of the treatment difference in HbA1c modelled out to at least 10 years when both treatment groups were assumed to be treated with insulin after 3 years (e) maintaining differences in serum lipids for the duration of the modelling exercise appears unjustified as it does not take into account the use of lipid lowering therapy and (f) analysis should have been carried out using the treatment policy estimand as opposed to the trial product estimand.

An incremental analysis of costs and QALYs was presented for oral semaglutide versus empagliflozin, sitagliptin and subcutaneous liraglutide, dulaglutide and semaglutide and these are outlined in Table 1. Given the concerns outlined above the ICERs estimated by the applicant (Table 1) are associated with significant uncertainty.

Table 1. Incremental cost-effectiveness of oral semaglutide 14mg daily versus comparators.

Comparator	Incremental costs (€)	Incremental QALYs	ICER/QALY (€)
Empagliflozin 25mg	1,272	0.12	10,332
Sitagliptin 100mg	1,119	0.26	4,342
Liraglutide 1.8mg sc.	-1,414	0.19	Semaglutide dominant
Dulaglutide 1.5mg sc.	-5	0.11	Semaglutide dominant
Semaglutide 1mg sc.	31	0.05	631

QALY: Quality adjusted life year; ICER: Incremental Cost Effectiveness Ratio; SC: subcutaneous. Figures in the table are rounded, and so calculations may not be directly replicable.

A probabilistic sensitivity analysis (PSA) was conducted with sampling around cohort characteristics, treatment effects, complication costs and utilities. The probability of oral semaglutide being cost effective at the €45,000/QALY threshold was approximately 69.2% v

empagliflozin, 89.9% v sitagliptin, 95.1% v liraglutide, 80.1% v dulaglutide and 59.2% versus once weekly subcutaneous semaglutide. A deterministic sensitivity analysis was also presented. The parameters that impacted the cost-effectiveness included: discount rate for benefits, time horizon, HbA1c reduction, treatment switching to basal insulin at HbA1c thresholds of 7% and 8% (compared with 7.5% in the base case analysis) and excluding disutilities associated with treatment administration. None of these parameters increased the ICER values above €20,000/QALY.

4. Budget impact

The estimated gross budget impact increased from €4,265,895 in year 1 to €31,649,449 in year 5 resulting in a cumulative 5 year gross budget impact of €91,848,833. The 5 year net budget impact was estimated at €28,568,101. When cost-offsets were included the 5 year net budget impact was estimated at €27,634,857.

5. Patient submissions

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

The NCPE Review Group consider empagliflozin to be the main comparator for the first oral GLP-1 receptor agonist semaglutide (Rybelsus®). This economic evaluation failed to satisfactorily demonstrate the cost-effectiveness of oral semaglutide as compared to empagliflozin mainly due to the inability to capture the long-term clinical outcomes associated with empagliflozin therapy. In view of this a price premium for oral semaglutide cannot be supported. The NCPE recommends that oral semaglutide (Rybelsus®) 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.