Cost-effectiveness of ocrelizumab (Ocrevus®) for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS)

The NCPE has issued a recommendation regarding the cost-effectiveness of ocrelizumab (Ocrevus®) for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS). Following assessment of the applicant's submission, the NCPE recommends that ocrelizumab (Ocrevus®) not be considered for reimbursement. 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 (Roche Products Ireland Ltd) economic dossier on the cost-effectiveness of ocrelizumab (Ocrevus®). 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 **October 2018**

Summary

On the 27th March 2018, Roche Products Ireland Ltd submitted an economic dossier on the clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of ocrelizumab (Ocrevus®) for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Ocrelizumab is a humanised monoclonal antibody that selectively targets CD20 a cell surface antigen expressed on B cells but not on lymphoid stem cells or plasma cells. It was granted regulatory approval from the European Medicines Agency (EMA) on the 8th January 2018. The formulation is ocrelizumab 300mg concentrate for solution for infusion. Each vial contains 300mg of ocrelizumab in 10ml at a concentration of 30mg/ml. The initial 600mg dose is administered as two separate intravenous infusions; first as a 300mg infusion followed 2 weeks later by a second 300mg infusion. Subsequent doses of ocrelizumab are administered as a single 600mg intravenous infusion every 6 months.

Multiple sclerosis (MS) is the most common chronic immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) characterised by focal plaques of primary demyelination and the presence of diffuse neurodegeneration in the grey and white matter of the brain and spinal cord. PPMS, which is the focus of this technology assessment, is a clinically distinct phenotype of MS and is characterised by steady irreversible progression of disability and neurological deterioration from disease onset without unequivocal recovery and occasional plateaus.

1. Comparative effectiveness of ocrelizumab (Ocrevus®)

The main clinical evidence to support the use of ocrelizumab in PPMS comes from one phase III clinical trial, ORATORIO, where 732 patients aged 18-55 years with an expanded disability status scale (EDSS) score of 3.0-6.5 points at screening and diagnosed PPMS according to the McDonald criteria were randomized to receive either ocrelizumab or

placebo. Ocrelizumab was administered as two 300mg infusions on day 1 and 15 for the first dose and as a single 600mg infusion thereafter. The primary endpoint was the time to onset of confirmed disability progression (CDP), over the double blinded treatment period (at least 120 weeks), defined as an increase in the EDSS score that was sustained for at least 12 weeks (CDP-12).

The results of the primary analysis demonstrate that treatment with ocrelizumab is associated with a statistically significant 24% reduction in the hazard for CDP for at least 12 weeks compared with placebo. The percentage of patients with 12-week CDP was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio: 0.76 [95% CI: 0.59, 0.98], p=0.0321). The magnitude of treatment effect associated with ocrelizumab on disability progression at 12 weeks was also demonstrated at 24 weeks as ocrelizumab was associated with a statistically significant reduction of 25% in the hazard for CDP for at least 24 weeks compared with placebo. The percentage of patients with CDP-24 (first secondary endpoint in the analysis hierarchy) was 29.6% with ocrelizumab versus 35.7% with placebo (hazard ratio: 0.75 [95% CI, 0.59, 0.98], p= 0.0365).

When missing EDSS results (n=21) were considered as having CDP events at either 12 or 24 weeks, the efficacy results were statistically significant; but when the missing events were not imputed, the results of the efficacy analysis were not statistically significant at CDP-12 and resulted in a reduced treatment effect (hazard ratio: 0.82; [95% CI, 0.63 to 1.07] p=0.1477). As with CDP-12, when the CDP-24 results were analysed without imputation, the CDP-24 results were not statistically significant (hazard ratio: 0.82 [95% CI, 0.62 to 1.10], p=0.1884) and therefore the disease progression efficacy results were sensitive to the method of imputation.

The efficacy data generated from the ITT population from the ORATORIO study is not reflective of the PPMS patient population identified in the product's license. The eligibility criteria of the ORATORIO trial restricted the study of ocrelizumab in PPMS patients less than 55 years of age and excluded those who are severely disabled i.e. those with an EDSS score of greater than 6.5. Therefore there may be uncertainty regarding the generalisability of the results generated to the Irish PPMS patient population. In addition, CDP at 12 and 24 weeks

as an outcome measure has no agreed effect size regarding a minimal clinically important difference.

Several members (n=6) of the CHMP considered the benefit-risk profile of ocrelizumab in the PPMS population to be negative owing to efficacy in the PPMS population having not been sufficiently established. The members outlined that '*a single confirmatory trial was conducted in this population. In the event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. The primary endpoint and most secondary endpoints were met; however, the demonstrated efficacy is not compelling from a statistical and clinical point of view. The pre-specified subgroup analyses as well as post hoc analyses suggest that a subgroup of patients with early PPMS and signs of acute inflammation may be the patient population most likely to benefit. However, these exploratory subgroup analyses are hypotheses generating and do not identify a patient population where efficacy has been sufficiently established.'*

The results of the other secondary endpoints for disability (T25-FW) and MRI (T2 lesion volume and change in total brain volume) outcomes supported the disease progression endpoints, demonstrating statistically significant efficacy of ocrelizumab when compared with placebo.

2. Safety of ocrelizumab (Ocrevus®)

The overall safety profile of ocrelizumab is based on data from patients from pivotal clinical trials in MS (RRMS and PPMS). The main safety issues with the use of ocrelizumab are infusion related reactions (IRR), an increased risk of infections and a higher frequency of malignancies in the ocrelizumab groups. Higher rates of serious infections were observed in ocrelizumab treated patients compared to interferon and placebo (6.2% versus 5.9%) treated patients. Ocrelizumab is contraindicated in patients with current active infection, cancer or in those who are severely immunocompromised. Hepatitis B virus screening should precede treatment and patients with active hepatitis B should not be treated with ocrelizumab. Vaccination with live-attenuated or live vaccines is not recommended during

treatment. The use of immunosuppressive drugs (other than corticosteroids) for symptomatic treatment of relapses is not recommended.

The occurrence of neoplasms is associated with ocrelizumab treatment. In the ORATORIO study neoplasms were reported in 11 of the 486 patients (2.3%) in the ocrelizumab group which included 4 cases of breast cancer, 3 cases of basal cell carcinoma and one case of endometrial adenocarcinoma, anaplastic large-cell lymphoma, malignant fibrous histiocytoma and pancreatic carcinoma. Between the cut-off dates for the two trials and the 30th June 2016 two additional cases of neoplasm (a basal cell skin cancer and squamous–cell carcinoma) were detected during the open-label extension study in which all patients received ocrelizumab.

In the OPERA I and II trials four neoplasms were reported in the ocrelizumab group including two cases of invasive ductal breast cancer, one renal cell carcinoma and one case of malignant melanoma while two cases occurred in the interferon beta-1a arm. Between the cut-off dates for the two trials and the 30th June 2016 five additional cases of neoplasm were detected during the open-label extension study including two cases of breast cancer, two cases of basal-cell skin cancer and one case of malignant melanoma.

As of 30th June 2016 the overall incidence rate of first neoplasm among patients treated with ocrelizumab across all studies involving patients with multiple sclerosis was 0.4 per 100 patient years of exposure to ocrelizumab as compared with 0.2 per 100 patient years of exposure in the pooled comparator groups.

3. Cost-effectiveness of ocrelizumab (Ocrevus®)

The cost-effectiveness of ocrelizumab was assessed using a multi-state cohort Markov model. The population considered in the economic model reflects the patient population recruited to the ORATORIO phase III clinical trial. The comparator included in the cost-effectiveness model is best supportive care (BSC), where 30% of patients are assumed to receive disease modifying therapies (DMT), which are not licensed for PPMS, and 70% of patients receive no treatment.

The cost-effectiveness model consists of 9 alive health states, designed to reflect and simulate disease progression for patients with PPMS over a lifetime. The mutually exclusive health states in the model represent and characterise differing levels of PPMS disability status according to the EDSS scale or death. The EDSS is a 10-point instrument that measures different areas of functional disability ranging from normal neurological examination at EDSS 0 to "confined to bed" at EDSS 9. The EDSS score of 10 was excluded from the model structure as mortality is dealt with separately.

Patients can transition between any of the 9 EDSS living health states during each cycle, with their condition in terms of disability either improving and resulting in a regression to a lower severity EDSS state or becoming worse and progressing to a higher EDSS state, or remaining the same, or transitioning to the absorbing health state - death. In each annual cycle patients who transition between EDSS states can either continue to receive ocrelizumab or BSC or withdraw from active treatment, or transition to death. In addition to disease progression the model takes into account mortality, treatment effect, treatment withdrawal and adverse events. It is assumed that treatment with ocrelizumab is discontinued once patients enter EDSS health state 7 or greater. The time horizon in the model is lifetime which is 50 years, and a one-year cycle length is applied to the model along with a half-cycle correction.

The probability of changing EDSS state in the natural history reference model which provided the underlying disease progression of patients who are on BSC was derived from the MSBase Registry. The treatment-adjusted model assumes to delay the progression of disease via hazard ratios which were derived from the ORATORIO data, using CDP-24 (6 month confirmed and sustained accumulation of disability) in the base case, which were applied to the natural history data probabilities for each EDSS health state.

The list price for ocrelizumab is €6,000 per 300mg vial and the recommended dose is 600mg twice yearly which results in a cost per patient per year of €22,680 ex VAT, or €28,200 including 23% VAT. The model incorporates cost data on drug acquisition, drug administration and monitoring costs, health states and adverse events.

In the applicant's base case scenario, the incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) was €146,860/QALY (incremental costs €93,318, incremental QALYs 0.64). The probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 0%.

As there are no licensed therapies available for PPMS patients in Ireland, the applicant conducted an advisory board in to seek advice from 10 Consultants who specialise in MS treatment from various Neurology departments across Ireland. All treatment options identified by the Neurology Consultants are prescribed off-label as none are licensed to treat PPMS. The outputs from the advisory board did not result in the identification or conclusion of a definitive treatment algorithm or estimate of the proportion of patients with PPMS who are in receipt of an unlicensed medicine.

The NCPE contacted several Neurology centres in Ireland to establish what is used in clinical practice in Ireland to identify the most appropriate comparator(s) relevant to the decision problem. The three largest treatment sites indicated their treatment preferences and the most likely comparator and the patient population in which unlicensed DMTs are prescribed.

The NCPE applied the results of their findings and consider that there are two possible scenarios for the comparator – one where 30% of patients receive DMT, and a second scenario where 30% of patients receive a rituximab biosimilar. In addition the NCPE explored the impact of alternative costs, transition probability assumptions, and treatment efficacy estimates on cost-effectiveness results.

For the first comparator, the NCPE implemented a number of changes to the model based on plausible alternative assumptions, resulting in increases in the ICER up to €277,579/QALY (incremental costs €105,323, incremental QALYs 0.38). At this ICER the probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 0%.

For the second comparator, the NCPE implemented a number of changes to the model based on plausible alternative assumptions, resulting in increases in the ICER up to €306,453/QALY (incremental costs €116,292, incremental QALYs 0.38). At this ICER the probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 0%.

The NCPE considers there to be significant uncertainty with both the applicant's base case scenario, and the NCPE alternative scenarios due to the results of the ORATORIO trial which are used in the cost-effectiveness model.

4. **Budget impact of ocrelizumab (Ocrevus®)**

Ocrelizumab is submitted for reimbursement under the National Drug Management Scheme. Ocrelizumab is available as a vial containing 300mg of ocrelizumab, and the proposed ex-manufacturer price of one vial is €6,000. The recommended dose of ocrelizumab is as per the license - 600mg administered as IV infusion every 6 months, 4 vials per year. The cost of ocrelizumab treatment per patient per year is €22,680 ex VAT and €28,200 including VAT.

The number of patients treated with ocrelizumab was estimated by the applicant to increase from 60 in year one to 198 by year five. Based on the applicant estimate of the current eligible population and assuming 30% of patients are currently treated with a disease modifying therapy, the projected gross budget impact of the drug acquisition over the first five years is €19.27 million including VAT. The net budget impact is €15.84 million including VAT.

In a second scenario that assumed 30% of patients are treated with a rituximab biosimilar, the projected net budget impact of the drug acquisition over the first five years is €18.35 million including VAT.

5. **A Patient Organisation Submission was received from Multiple Sclerosis Ireland.**

6. Conclusion

Following assessment of ocrelizumab (Ocrevus®) for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity, the NCPE recommends that ocrelizumab (Ocrevus®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.