Cost-effectiveness of ocrelizumab (Ocrevus®) for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS)

The NCPE has issued a recommendation regarding the cost-effectiveness of Ocrelizumab (Ocrevus) for the treatment of relapsing – remitting multiple sclerosis (RRMS). Following assessment of the applicant's submission, the NCPE recommends that ocrelizumab (Ocrevus®) 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 (Roche Products Ireland Ltd) economic dossier on the cost effectiveness of Ocrelizumab for RRMS. 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 **August 2017**

Summary

Roche Products Ireland Ltd submitted an economic dossier on the cost-effectiveness of ocrelizumab (Ocrevus®) for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) on the 16th March 2018. 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 11th 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 a disabling autoimmune disease where immune cells target central nervous system (CNS) antigens, leading to demyelination, glial activation and subsequent loss of neurones and axons. RRMS, which is the subject of this economic assessment, is the most common MS disease course and 86% - 93% of patients with MS are initially diagnosed with RRMS. It will eventually transition to SPMS with approximately 50% developing SPMS within 20 years of the onset of RRMS.

Patients with MS may develop autonomic, visual, motor and sensory deficits. Initial symptoms in RRMS may include optic neuritis (predominantly unilateral) in about 25% of cases, brainstem events (approx. 45%) and partial spinal cord syndromes, often sensory involving sphincter and/or sexual dysfunction. Symptoms during relapse may include numbness, tingling, pain, weakness, vision loss, gait impairment, incoordination, imbalance and bladder dysfunction. Diagnosis of MS is based on clinical findings supported by MRI scanning (demonstration of T2 hyperintense lesions and gadolinium enhancing T1 lesions), the presence of oligoclonal bands in the cerebrospinal fluid (CSF) and abnormal visual evoked responses.

1. Comparative effectiveness

The main clinical evidence to support the use of ocrelizumab in RRMS comes from two identical phase III clinical trials where 1,656 patients with relapsing MS were randomised to receive intravenous ocrelizumab 600mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 44µg three times weekly for 96 weeks. Ocrelizumab was administered as two 300mg infusions on days 1 and 15 for the first dose and as a single 600mg infusion thereafter. In the OPERA I trial, 821 patients from 141 trial sites across 32 countries were randomised between the 31st August 2011 and the 14th February 2013 whilst 835 patients from 166 trial sites across 24 countries were randomised between the 20th September 2011 and the 28th March 2013 in OPERA II. The primary end point was the annualised relapse rate (ARR) by 96 weeks and there were 10 hierarchically ordered secondary end points.

The ARR at 96 weeks was 0.16 in the ocrelizumab arm and 0.29 in the interferon beta-1a arm in both OPERA I and in OPERA II trials, representing a 46% and 47% lower ARR respectively ($p<0.001$ for both comparisons). In the prespecified pooled analysis the percentage of patients with disability progression at 12 weeks was 9.1% in the ocrelizumab group versus 13.6% in the interferon beta-1a group representing a 40% lower risk with ocrelizumab ($p<0.001$). Corresponding figures for the rate of disability progression confirmed at 24 weeks were 6.9% and 10.5% respectively again showing a 40% risk reduction ($p=0.003$). The percentage of patients with disability improvement at 12 weeks was 20.7% in the ocrelizumab group as compared with 15.6% in the interferon beta-1a group (33% higher rate of improvement with ocrelizumab; $p=0.02$). The effect of ocrelizumab on the rate of confirmed disability improvement was significant in OPERA I but not in OPERA II. It is seen that in the pooled analysis all the primary and secondary end points significantly favoured ocrelizumab over interferon beta-1a.

The difference in the adjusted mean change in the Multiple Sclerosis Functional Composite score from baseline to week 96 between the ocrelizumab group and the interferon beta-1a group was 0.04 in the OPERA I trial ($p=0.33$ which was the first nonsignificant p value in the hierarchical testing) and 0.11 in the OPERA II trial ($p=0.004$). In the intention to treat population 47.9% of patients in the ocrelizumab group had no evidence of disease activity

by 96 weeks as compared with 29.2% in the interferon beta-1a group in the OPERA I trial, corresponding figures for the OPERA II trial were 47.5% and 25.1% respectively however these findings were considered nonconfirmatory.

For MRI related secondary end points the total mean number of gadolinium enhancing lesions (GAL) per T1 weighted MRI scan in the OPERA I trial was 0.02 with ocrelizumab versus 0.29 with interferon beta-1a (94% lower number of lesions, $p<0.001$) and in OPERA II the values were 0.02 versus 0.42 respectively, $p<0.001$. The total mean number of new or newly enlarged lesions per T2 weighted MRI scan in the OPERA I trial was 0.32 with ocrelizumab versus 1.41 with interferon beta-1a (77% lower number of lesions with ocrelizumab, $p<0.001$). Corresponding values for OPERA II were 0.33 versus 1.9 (83% lower with ocrelizumab, $p<0.001$). The total mean number of new hypointense lesions on T1 weighted MRI in the OPERA I trial was 0.42 with ocrelizumab versus 0.98 with interferon beta-1a (57% lower number of lesions with ocrelizumab, $p<0.001$). The values for OPERA II were 0.45 and 1.26 respectively, $p<0.001$.

2. Safety

The main safety data comes from the OPERA I and OPERA II studies and from the ORATORIO study in patients with PPMS. Over 80% of patients in OPERA I and II reported an adverse event to ocrelizumab which was similar to the rate of adverse events with the comparator interferon beta-1a. The most common adverse events to ocrelizumab were infusion-related reaction , nasopharyngitis, upper respiratory tract infection, headache and urinary tract infection. Serious adverse events were reported in 6.9% and 7% of patients treated with ocrelizumab in OPERA I and II respectively. In the OPERA trials the reported rate of upper respiratory tract infection (15.2% v 10.5%) and nasopharyngitis (14.8% v 10.2%) were higher for ocrelizumab as compared with interferon beta-1a. Across the two trials the percentage of patients reporting herpesvirus-associated infection was 5.9% in the ocrelizumab group and 3.4% in the interferon beta-1a group. Infusion related reactions occurred in 34.3% of patients in the OPERA studies as compared with 9.7% in the interferon beta-1a arm.

The occurrence of neoplasms is associated with ocrelizumab treatment. 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. 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 clinical cut-off date (24th July 2015) and June 30th 2016 two additional cases of neoplasm (a basal cell skin cancer and squamous –cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab. Two cases (cervical adenocarcinoma in situ and squamous cell carcinoma) were reported in the 239 patients in the placebo group of the ORATORIO trial. As of June 30th 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. The manufacturer highlights that continued follow-up in the open-label extension periods has not shown increased incidence rates of malignancy with additional exposure to ocrelizumab, which remains within the range of placebo-treated patient data from MS clinical trials and epidemiological data of MS patients.

3. Cost effectiveness

The population in the economic model reflects the therapeutic indication i.e. patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features. In the pivotal clinical trials 75% of the treated population had not received previous disease modifying therapy (DMT) so ocrelizumab may be used as first line DMT in RRMS. The comparators included in the cost-effectiveness model are all disease modifying therapies which are licensed for use in RRMS and are currently reimbursed in Ireland. The cost effectiveness of ocrelizumab was assessed using a cohort multi-state Markov model

developed to reflect health states based on disease classification and severity. The model time horizon is over 50 years and a half cycle correction is applied. The Markov model structure has been designed to account for both MS relapses and disability progression.

Health states in the model are defined by the EDSS giving rise to 10 health states (EDSS 0 – 9). Patients enter the model in a baseline RRMS disease-course state on active treatment. In each cycle patients may (i) transition between EDSS states in RRMS (ii) withdraw from active treatment and continue to receive best standard care (iii) convert to SPMS and then transition between EDSS states in SPMS or (iv) transition to death. Relapse rate, conversion from RRMS to SPMS and mortality are all EDSS dependent as are costs and health related quality of life.

The probability of changing EDSS state was determined by natural history data and treatments were assumed to delay the progression of disease and reduce the frequency of relapses in RRMS. Treatment effects in the form of hazard ratios were derived from the mixed treatment comparison, using CDP-12 in the base case and applied to the natural history data probabilities of worsening in EDSS. The annual relapse rate (ARR) within each RRMS and SPMS EDSS was determined using natural history and treatment effects for patients within RRMS were taken from the network meta-analysis (NMA). In relation to natural history and treatment effect the British Columbia (BC) database was the preferred source and was applied in the model basecase for transition probabilities in RRMS. Results in the base case represent the perspective of the Health Service Executive (HSE). Health outcomes in the economic evaluation were expressed as quality adjusted life years i.e. QALYs. Utility data was identified from the pivotal clinical trials (OPERA I and OPERA II), the published literature and recent HTA submissions to NICE. The list price for ocrelizumab is € 6,000 per 300mg vial and the recommended dose is 600mg twice yearly. This results in a cost per patient per year of € 22,680. It is subject to VAT at 23% which would result in an annual cost of € 28,200 per patient (which does not include administration costs). The economic dossier presents the reimbursement cost per patient for each of the comparators at the recommended dose. The model incorporates cost data on drug acquisition, drug administration and monitoring costs, health states and adverse events. A discount rate of

5% was applied in line with current guidelines and incremental cost-effectiveness ratio (ICER) values are shown in the table below.

Drug	**Incremental cost-effectiveness ratio (ICER) versus Ocrelizumab**
Alemtuzumab	Alemtuzumab dominates (less costly, more effective)
Interferon beta-1a (Avonex)	€42,433/QALY
Dimethyl fumarate	€40,432/QALY
Fingolimod	Ocrelizumab dominant
Glatiramer acetate	€39,532/QALY
Interferon beta-1b	€34,580/QALY
Natalizumab	Ocrelizumab dominant
Peginterferon beta-1a	€62,445/QALY
Interferon beta-1a sc	€52,756/QALY
Teriflunomide	€49,124/QALY

The NCPE review group highlighted the uncertainty around these cost-effectiveness estimates particularly the confirmed disability progression (CDP) and the time horizon. The ICER values exceed €100,000/QALY against many of the comparators when the upper confidence interval values of CDP are used. Similarly, many of the ICERs for ocrelizumab versus comparators exceeded €100,000/QALY at the 10 year time horizon. In the submitted economic model it was assumed that the beneficial effects of ocrelizumab would remain for the 50 year time horizon.

4. Budget impact

The number of patients treated with ocrelizumab was estimated to increase from 130 in year one to 736 by year five. The gross budget impact was predicted to increase from €3,680,808 in year 1 to €20,792,478 in year 5. The cumulative 5 year gross budget impact

was estimated at €66,481,945 with a net 5 year budget impact predicted to be in the region of €21,934,313.

5. Conclusion

As ocrelizumab may be used as a first line treatment for RRMS the NCPE recommends that ocrelizumab should 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.