CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Ocrelizumab (Ocrevus – Hoffmann-La Roche Limited)

Indication: Management of adult patients with early primary progressive multiple sclerosis (PPMS) as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee recommends that ocrelizumab be reimbursed for the management of adult patients with early PPMS as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity, if the following criteria and conditions are met:

Clinical criteria:
- Therapy may be initiated if the patient: is between 18 and 55 years old; has a confirmed diagnosis of PPMS (based on McDonald criteria 2010), with an Expanded Disability Status Scale (EDSS) score between 3.0 and 6.5; a score of at least 2.0 on the Functional Systems scale for the pyramidal system due to lower extremity findings; and a disease duration of less than 15 years for those with an EDSS greater than 5.0 or less than 10 years for those with an EDSS of 5.0 or less.
- Treatment should be discontinued for patients with an EDSS score of equal to or greater than 7.0.

Conditions:
- The patient is under the care of a specialist with experience in the diagnosis and management of multiple sclerosis.
- There is a reduction in price.

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OCRELIZUMAB (OCREVUS — HOFFMANN-LA ROCHE LIMITED)

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Criteria:

- Therapy may be initiated if the patient: is between 18 and 55 years old; has a confirmed diagnosis of PPMS (based on McDonald criteria 2010), with an Expanded Disability Status Scale (EDSS) score between 3.0 and 6.5; a score of at least 2.0 on the Functional Systems scale for the pyramidal system due to lower extremity findings; and a disease duration of less than 15 years for those with an EDSS greater than 5.0 or less than 10 years for those with an EDSS of 5.0 or less.
- Treatment should be discontinued for patients with an EDSS score of equal to or greater than 7.0.

Conditions:

- The patient is under the care of a specialist with experience in the diagnosis and management of multiple sclerosis (MS).
- There is a reduction in price.

Reasons for the Recommendation:

1. One double-blind, phase III, randomized controlled trial (RCT) (ORATORIO, N = 732) demonstrated that ocrelizumab was superior to placebo for reducing the risk of confirmed disability progression (CDP) lasting at least 12 weeks (hazard ratio: 0.76; 95% confidence interval [CI], 0.59 to 0.98) and CDP lasting at least 24 weeks (hazard ratio: 0.75; 95% CI, 0.58 to 0.98).
2. The manufacturer-submitted unit price for ocrelizumab is $8,150 per 300 mg vial, which equates to an average annual cost of $32,600. Based on reanalysis of the manufacturer's base case by the CADTH Common Drug Review (CDR), ocrelizumab compared with best supportive care (BSC) is associated with an incremental cost of $588,143 per quality-adjusted life-year (QALY) gained; therefore it is not a cost-effective treatment for adult patients with PPMS. The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of up to $200,000 per QALY gained was 0%. CADTH reanalysis suggested that an 82% reduction in the submitted price would be required to achieve an incremental cost per QALY of $50,000.

Of Note:

1. The initiation criteria are based on the inclusion criteria for ORATORIO. The discontinuation criterion is based on input from clinicians with expertise in the management of PPMS and data inputs in the manufacturer-submitted economic model (it was assumed that patients who reached an EDSS score of 7 or greater while on treatment with ocrelizumab would discontinue treatment).
2. ORATORIO enrolled patients aged 18 years to 55 years and those with an EDSS score of 3.0 to 6.5. The manufacturer is planning a five-year, multi-centre, phase IIIb, double-blind, placebo-controlled RCT to further evaluate the efficacy and safety of ocrelizumab in PPMS patients. The details have not be finalized, though it is expected that the study will provide evidence regarding the use of ocrelizumab in patients between 55 years and 65 years of age as well as patients with an EDSS score between 6.5 and 8.0.
3. CDEC noted that the lack of long-term safety evidence for ocrelizumab creates uncertainty with regard to its assessment of benefits versus harms. Ocrelizumab is associated with serious infusion-related reactions and increased risk of infections (overall

and opportunistic infections). Progressive multifocal leukoencephalopathy (PML) has been associated with disease-modifying therapies (DMTs) for MS. One case of PML has been reported for a patient who was treated with ocrelizumab; however, this patient had also received prior treatment with natalizumab for three years. The clinical experts consulted by CADTH noted that specialized monitoring for PML would not likely occur for patients treated with ocrelizumab. Ocrelizumab may also be associated with an increased risk of malignancy. Patients with a strong family history of cancer, or older patients, may not be good candidates for ocrelizumab given the possibility of an increased cancer risk. An informed discussion would be needed between patient and prescriber.

4. The development of inflammation in PPMS is unpredictable and there are currently no guidelines for determining how frequently a patient with PPMS should be monitored for active inflammation with gadolinium (Gd)-enhanced magnetic resonance imaging (MRI). The evidence regarding potential toxicity from cumulative Gd exposure is evolving. Therefore, decisions regarding optimal MRI monitoring should be made by clinicians with expertise in the diagnosis and management of MS.
5. There is considerable uncertainty associated with the estimates of cost-effectiveness due to limitations with the clinical data, unknown long-term harms and efficacy with ocrelizumab, and limitations with the economic analysis submitted to CADTH. Ocrelizumab had a 0% probability of being cost-effective at willingness-to-pay thresholds up to $200,000 per QALY. CADTH reanalysis suggests that an 80% reduction in the submitted price would lead to an incremental cost per QALY of $68,378.

Other Discussion Points:

- Ocrelizumab is the first DMT approved by Health Canada for treating patients with PPMS. Therefore, BSC was an appropriate comparator in ORATORIO.
- Ocrelizumab received a Notice of Compliance with Conditions from Health Canada for the PPMS indication. Health Canada considered evidence from the lone pivotal trial (ORATORIO) insufficient for a full Notice of Compliance; it is requiring the manufacturer to conduct an additional well-designed confirmatory study to confirm the efficacy of ocrelizumab.
- The use of MRI to monitor inflammatory activity in clinical practice may increase with ocrelizumab, which was not considered in the manufacturer's economic evaluation.
- Additional research is needed to assess the long-term safety and toxicity associated with Gd exposure and potential accumulation of Gd in the central nervous system.

Background:

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells. It has been approved by Health Canada for use in the following indications:

- Treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features
- Management of adult patients with early PPMS as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

The recommended dose of ocrelizumab is 600 mg IV once every six months. The product monograph recommends that the initial 600 mg dose be administered as two separate IV infusions: 300 mg for the first infusion, followed by a second 300 mg infusion two weeks later. It is available as single-use vials containing 300 mg of active substance.

The current CDR submission for ocrelizumab is for use in the treatment of patients with PPMS. CADTH has previously reviewed ocrelizumab for use in the treatment of adult patients with RRMS.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CADTH: a systematic review of RCTs of ocrelizumab and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from a clinical expert with experience treating patients

with MS, and patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by PPMS.

Patient Input Information

One patient group (the Multiple Sclerosis Society of Canada) responded to the call for patient input for this CDR review. Information was gathered primarily through an online survey. The following is a summary of key input from the perspective of the patient group:

- PPMS is a devastating form of MS that is characterized by continual worsening of the disease. Patients experience progressive disability, fatigue, cognitive impairment, weakness, spasticity, tremor, poor coordination, bladder and bowel problems, sexual dysfunction, depression, pain, dizziness, visual issues, and issues with speech and swallowing. As the disease progresses, PPMS patients often lose their ability to participate in physical activities, social engagements, and employment.
- Ocrelizumab is the first treatment approved for use in patients with PPMS. All other treatment options and therapies for PPMS aim to control symptoms rather than to modify the course of the disease. As such, patients feel there is a significant unmet need for those living with PPMS, and are looking for any treatment options that could potentially slow or stop the progression of the disease.

Clinical Trials

The CADTH systematic review included one phase III, multinational, multi-centre, parallel-group, double-blind, placebo-controlled RCT. Patients enrolled in the ORATORIO trial (N = 732) were randomized (2:1) to receive IV infusions of ocrelizumab or placebo every six months (as two infusions 14 days apart). Patients aged 18 years to 55 years with PPMS were eligible for enrolment if they had an EDSS score between 3.0 and 6.5 and a score of at least 2.0 on the Functional Systems scale for the pyramidal system that was due to lower extremity findings. The diagnosis of PPMS was made in accordance with the revised 2005 McDonald criteria. Patients also had to have a disease duration of less than 15 years for those with an EDSS greater than 5.0 or less than 10 years for those with an EDSS of 5.0 or less at screening.

Key limitations with the ORATORIO trial included: sensitivity of the results for 12-week CDP (primary end point), 24-week CDP (secondary end point), and the Timed 25-Foot Walk (T25FW) to different methods and assumptions regarding the imputation of missing data; the unplanned increase in sample size (i.e., from 630 to 732); the large and disproportionate rate of withdrawal across the study (i.e., 33.6% and 20.7% in the placebo and ocrelizumab groups, respectively); the potential for unblinding due to the adverse event (AE) profile of ocrelizumab (particularly events related to the administration of the study drug); and the need to impute a large amount of the data for some end points (e.g., Short Form (36) Health Survey [SF-36] and changes in MRI end points). Generalizability of the results may be limited by: the exclusion of patients more than 55 years of age and those with an EDSS score above 6.5; the uncertainty regarding the proportion of Canadian PPMS patients who would have evidence of active inflammation in the brain and/or spinal cord; and the extensive contact with health professionals during the study.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- CDP: Time to CDP for 12 weeks was the primary end point of the study. Time to CDP for at least 24 weeks was a secondary end point. Disability progression was defined as an increase in a patient's EDSS score of at least 1.0 from baseline when the baseline score was ≤ 5.5; or an increase of 0.5 from baseline when the baseline score was > 5.5. Disability progression was considered to be confirmed when the increase from baseline in EDSS was documented at a regularly scheduled clinic visit at least 12 weeks or 24 weeks after the patient's neurological worsening was initially documented.
- T25FW assessment: Time required for the patient to walk a 25-foot course as quickly as possible, then time required to repeat the course once. The T25FW score is the average of the two completed trials. A change of at least 20% in the T25FW score is commonly cited as the minimal clinically important difference for patients with MS.
- MRI end points: Efficacy end points that were evaluated using MRI included change in brain volume from week 24 to week 120; change in volume of T2 lesions from week 24 to week 120; total number of new or newly enlarged T2 hyperintense lesions by week 120; and total number of new T1 Gd-enhancing lesions by week 120.

- Multiple Sclerosis Functional Composite: Includes three objective, quantitative continuous scales that assess leg function and ambulation (the T25FW), arm and hand function (the 9-Hole Peg Test [9-HPT]), and cognitive function (the 3-second Paced Auditory Serial Addition Test [PASAT-3]).
- SF-36: a 36-item generic health status measure. It measures eight general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Higher scores indicate better health-related quality of life. Each of the eight sub-domains is measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The SF-36 items can be analyzed in two categories: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Efficacy

Treatment with ocrelizumab was associated with a statistically significant reduction of 24% in the hazard for CDP for at least 12 weeks (hazard ratio: 0.76; 95% CI, 0.59 to 0.98). The results in the intention-to-treat population were sensitive to the method of imputation that was used to account for patients who experienced an initial progression event, but withdrew prior to having the event confirmed at least 12 weeks later. When these patients were considered as having CDP events, the results were statistically significant; but when these events were not imputed, the results were no longer statistically significant (hazard ratio: 0.82; 95% CI, 0.63 to 1.07). Ocrelizumab was statistically significantly superior to placebo in reducing 12-week CDP only in the subgroup of patients who were less than 45 years of age at baseline (hazard ratio: 0.64; 95% CI, 0.45 to 0.92). Reductions in 12-week CDP with ocrelizumab versus placebo were observed in other subgroups of interest. Interaction tests for the univariate subgroup analyses were not statistically significant. The multivariate analysis also demonstrated no statistically significant interaction effects.

Ocrelizumab was associated with a statistically significant reduction of 25% in the hazard for CDP for at least 24 weeks compared with placebo (hazard ratio: 0.75; 95% CI, 0.59 to 0.98). Similar to 12-week CDP, when analyzed without imputation, the results were no longer statistically significant (hazard ratio 0.82; 95% CI, 0.62 to 1.10). The rates of 12-week and 24-week CDP events in the ocrelizumab and placebo groups showed initial separation in the 12-week to 18-week range, then remained relatively constant between the two groups for approximately two years before showing additional separation beginning at approximately week 120.

Treatment with ocrelizumab was associated with reductions in the following compared with placebo: T2 lesion volume ($P < 0.0001$), rate of new and enlarging T2 hyperintense lesions (adjusted rate ratio: 0.081; 95% CI, 0.058 to 0.111); rate of T1 Gd-enhancing lesions (adjusted rate ratio: 0.024, 95% CI, 0.011 to 0.051), and brain volume loss (relative difference: 17.475%; 95% CI, 3.206 to 29.251).

T25FW times increased in both groups throughout the trial. There was a statistically significant difference between the ocrelizumab and placebo groups (relative reduction of 29.337%; 95% CI, –1.618 to 51.456; $P = 0.0404$). At week 120, the absolute difference between the placebo and ocrelizumab groups in mean change in T25FW time was 3.03 seconds (increase of 11.76 seconds in the placebo group and 8.79 seconds in the ocrelizumab group).

Change from baseline to week 120 in the SF36-PCS was a pre-specified secondary end point, and there was no statistically significant difference between the ocrelizumab and placebo groups (least squares mean difference [LSMD]: 0.377; 95% CI, –1.048 to 1.802; $P = 0.6034$). Ocrelizumab-treated patients demonstrated an improvement in mean SF-36 MCS, whereas those treated with placebo experienced a reduction in mean SF-36 MCS (LSMD: 3.318; 95% CI, 1.414 to 5.221; $P = 0.0007$).

Harms (Safety and Tolerability)

Nearly all patients experienced at least one AE during the double-blind phase of the ORATORIO study (95.1% in the ocrelizumab group and 90.0% in the placebo group). Infections and infestations were the most frequently reported category of AE, with a similar frequency in the ocrelizumab and placebo groups (69.8% and 67.8%, respectively).

Serious adverse events (SAEs) were reported for 22.2% of patients in the placebo group and 20.4% of those in the ocrelizumab group. The overall rate of SAEs was 11.67 per 100 patient-years in the placebo group and 10.24 per 100 patient-years in the ocrelizumab group. The proportion of patients who experienced an SAE that was categorized as an infection or infestation was

similar in both the ocrelizumab and placebo groups (6.2% versus 5.9%). The proportion of patients with an SAE that was categorized as a neoplasm was greater in the placebo group compared with the ocrelizumab group (2.9% versus 1.6%).

AEs leading to withdrawal from the study treatments occurred for 4.1% of patients in the ocrelizumab group and 3.3% in the placebo group. Cancers were the most frequently reported category of AE leading to discontinuation from the ocrelizumab group (1.4% versus 0.4% in the placebo group). The proportion of patients who withdrew as a result of an infection was slightly lower in the ocrelizumab group compared with the placebo group (0.8% versus 1.3%). A greater proportion of ocrelizumab-treated patients experienced at least one AE that led to a modification or interruption of the study treatment compared with placebo (9.7% versus 5.0%).

Infusion-related reactions were more commonly reported in the ocrelizumab group compared with the placebo group (39.9% versus 25.5%). The most commonly reported symptoms associated with infusion-related AEs in the ocrelizumab group were pruritus, flushing, rash, pyrexia, headache, and throat irritation. Nearly all of the infusion-related AEs were mild or moderate in severity (98.8% in the ocrelizumab group and 98.3% in the placebo group were grade 1 or grade 2 events). The proportion of patients who withdrew as a result of an infusion-related reaction was 0.4% in both the placebo and ocrelizumab groups.

Malignancies were reported in a greater proportion of ocrelizumab-treated patients (11 patients [2.3%]; 13 events) compared with placebo-treated patients (two patients [0.8%]; two events). The rate of malignancy was 0.92 per 100 patient-years (95% CI, 0.49 to 1.57) in the ocrelizumab group and 0.30 per 100 patient-years (95% CI, 0.04 to 1.10) in the placebo group. The most commonly reported malignancies included breast cancer in women (four ocrelizumab-treated patients and no placebo-treated patients) and basal cell carcinoma (three ocrelizumab-treated patients and one placebo-treated patient).

Cost and Cost-Effectiveness

Ocrelizumab is available as 300 mg single-use vials for infusion at the manufacturer-submitted price of $8,150 per vial. At the recommended dose of 600 mg every six months, the annual cost of ocrelizumab is $32,600 per patient.

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing ocrelizumab with BSC in adult patients with PPMS. BSC comprised outpatient visits, rehabilitation, hospitalizations, and medication for symptom management, and was chosen as the sole comparator as there are no licensed pharmacological treatments for PPMS in Canada. In the model, PPMS patients transitioned between EDSS states 0 through 9. In each cycle, patients could transition to the absorbing death state, with the probability of death varying by disease severity. It was assumed that patients who reached an EDSS score of 7 or greater while on treatment with ocrelizumab would discontinue treatment. The analysis was run over a lifetime time horizon (up to an age of 100 years) using an annual cycle length. The analysis was based on a Canadian public health care system perspective. In the base-case analysis, the manufacturer reported that ocrelizumab was costlier and more effective than BSC. The incremental QALY gain was 0.72 and the increase in health care costs was $206,957, leading to an incremental cost per QALY gained of $285,741. The probability that ocrelizumab was cost-effective given a willingness-to-pay threshold of $50,000 per QALY was 0%.

CADTH identified a number of limitations with the submitted economic model:

- Data relating to mortality were derived from sources that were not specific to patients with PPMS and likely included predominantly RRMS patients. There were also concerns over how mortality multipliers obtained from these sources were derived and incorporated into the model. The relevance of this data (likely reflective of an RRMS patient population and associated disease severity) to the current Canadian PPMS patient population is limited.
- Natural history data were derived from a data set that implied that untreated patients could experience an improvement in EDSS state. The clinical expert consulted by CADTH did not accept that this was likely, given the nature of the condition.
- Utility values used in the model lacked face validity, particularly for EDSS states 8 and 9 (values less than zero).
- Other parameters of uncertainty included the use of cost data for RRMS and the apparent disregard for the potentially increased risk of cancer.

CADTH reanalysis accounting for the identified limitations (mortality multipliers, assumption of improvement in EDSS state, utility values) resulted in in an incremental cost-utility ratio for ocrelizumab of $588,143 when compared with BSC. The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of up to $200,000 per QALY gained was 0%. CADTH reanalysis suggested that an 82% reduction in the submitted price would be required to achieve an incremental cost per QALY of $50,000.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 21, 2018 Meeting

Regrets:

None

Conflicts of Interest:

None