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CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**OCRELIZUMAB (OCREVUS – HOFFMANN-LA ROCHE LIMITED)**
Indication: Treatment of adult patients with relapsing-remitting multiple sclerosis with active disease defined by clinical and imaging features.

**RECOMMENDATION:**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ocrelizumab be reimbursed for the treatment of relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features, if the following conditions are met:

**Conditions:**
- patient under the care of a specialist with experience in the diagnosis and management of multiple sclerosis (MS)
- reduction in price of at least 50%.


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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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## Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ocrelizumab be reimbursed for the treatment of relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features, if the following conditions are met.

## Conditions:

- The patient is under the care of a specialist with experience in the diagnosis and management of multiple sclerosis (MS).
- The price is reduced at least 50%.

## Reasons for the Recommendation:

1. Two double-blind, phase III, randomized controlled trials (RCTs) (OPERA-I and OPERA-II) demonstrated that ocrelizumab was superior to interferon beta-1a for reducing the annualized relapse rate (ARR), with a rate ratio of 0.536 (95% confidence interval [CI], 0.400 to 0.719) in OPERA-1, 0.532 (95% CI, 0.397 to 0.714) in OPERA-II, and 0.535 (95% CI, 0.435 to 0.659) in the pooled analysis. The rate of relapse with ocrelizumab was 46% lower than with interferon beta-1a in OPERA-I and 47% lower in both OPERA-II and the pooled analysis. A greater proportion of ocrelizumab-treated patients remained free of relapses at 96 weeks compared with those in the interferon beta-1a group in both OPERA-I (80% versus 67%, respectively; relative risk [RR] 1.20 [95% CI, 1.10 to 1.31]) and OPERA-II (79% versus 64%, respectively; RR 1.23 [95% CI, 1.12 to 1.35]).
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 CADTH Common Drug Review (CDR), ocrelizumab was not a cost-effective treatment for adult patients with RRMS, regardless of a decision-maker's willingness to pay for a gain in quality-adjusted life-years (QALYs). It has a 2.0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY, and a 12.9% probability of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY. At a price reduction of at least 50% of the submitted price, the probability that ocrelizumab is cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 81%.

## Of Note:

- The majority of patients in OPERA-I and OPERA-II had no exposure to any MS treatments in the previous two years. However, it was unclear whether those who had no exposure to a disease-modifying therapy for RRMS in the two years before these trials had received any MS treatments at all, or whether they were completely naive to disease-modifying therapy. In the latter case, ocrelizumab could be considered a first-line therapy; in the former case, second-line therapy would be more appropriate. The manufacturer is currently conducting two open-label, uncontrolled, phase IIIb studies (CHORD and CASTING) to evaluate the efficacy and safety of ocrelizumab in patients with RRMS who have demonstrated a suboptimal response to a disease-modifying treatment.
- Glatect (subsequent-entry glatiramer acetate) received a recommendation for reimbursement, with clinical criteria and conditions, by CDEC (July 2017) for use in patients with RRMS for whom glatiramer acetate is considered the most appropriate treatment option. Teva-glatiramer, another glatiramer acetate product, has received a Health Canada indication for the treatment of RRMS and may become available for reimbursement. CDEC noted that the availability of less costly drugs – such as subsequent-entry glatiramer acetate – could alter the optimal choice among RRMS therapies, including ocrelizumab, on the basis of cost.
- CDEC noted that the lack of long-term safety evidence for ocrelizumab creates uncertainty with respect to the long-term added value of ocrelizumab relative to other disease-modifying therapies for RRMS.

## Discussion Points:

- CDEC discussed the appropriateness of the comparator treatment used in the OPERA studies. It also discussed with an expert involved in the CDR review of ocrelizumab that interferon beta-1a may not be the optimal choice for a comparative treatment. However, it acknowledged that the treatment differences, especially with respect to ARR, were likely clinically significant. The incremental clinical benefits and risks in comparison with other available disease-modifying therapies for RRMS are uncertain.

## Background:

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets B cells that express CD20. It is indicated for use as monotherapy for the treatment of RRMS in adult patients with active disease defined by clinical and imaging features. The recommended dose of ocrelizumab is 600 mg intravenous (IV) once every six months. The product monograph recommends that the initial 600 mg dose be administered as two separate IV infusions: a first infusion of 300 mg, followed by a second infusion of 300 mg two weeks later.

## Summary of CDEC Considerations:

The Committee considered the following information prepared by CADTH CDR: a systematic review of RCTs of ocrelizumab, two indirect comparisons, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues important to patients who are living with MS and their caregivers.

## Patient Input Information:

One patient group (the Multiple Sclerosis Society of Canada) responded to the call for patient input. Information for the submission was gathered from a survey and from publicly available information. The following is a summary of key input from the patient group:

- Those living with MS commonly experience fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Other symptoms may include issues with balance, sexual dysfunction, spasticity, tremor, weakness, and difficulty speaking and swallowing. These symptoms can have a profound effect on an individual's quality of life.
- The episodic nature of MS creates unique employment issues – many people are unable to maintain stable jobs or to remain in the workplace due to relapses, symptoms, medication side effects, and disability progression. In addition to affecting employment, MS can interfere with, or pose a barrier to, education, physical activity, family commitments, interpersonal relationships, and social and recreational life.
- Caregivers play an instrumental role in the overall care management plan of people living with MS, especially those living with highly active or progressive disease. A caregiver's role can range from providing emotional support and assistance with medication administration, to helping with activities of daily living such as personal care, feeding, and transportation to and from appointments.
- There is no standard MS treatment algorithm. It is very common for a treatment to work well in one individual but fail in another. Having access to different treatment options is critical for people affected by MS in order to maintain their quality of life and control their MS as effectively as possible.

### Clinical Trials

The CDR systematic review included two identically designed, multi-centre, parallel-group, double-blind, double-dummy, active-comparator, phase III RCTs. Patients enrolled in the OPERA-I (N = 821) and OPERA-II (N = 835) studies were randomized (1:1) to receive ocrelizumab 600 mg IV once every six months or interferon beta-1a 44 mcg subcutaneously three times per week. The studies evaluated clinical end points (e.g., relapse), magnetic resonance imaging (MRI) end points (e.g., changes in lesions on T1- and T2-weighted scans), and patient-reported end points (e.g., Short Form [36] Health Survey [SF-36]). During the 96-week treatment period, study participants were required to attend 10 scheduled assessment visits. Additionally, structured telephone interviews were conducted every four weeks starting at week 8 to identify any new or worsening neurological symptoms that would require an unscheduled clinic visit and to collect data on possible infections.

Patients aged 18 to 55 years with a relapsing form of MS were eligible for the OPERA-I and OPERA-II studies if they had a Kurzke Expanded Disability Status Scale (EDSS) score between 0 and 5.5 at the time of screening, at least two documented clinical relapses within two years of screening or one relapse within one year of screening, an MRI scan showing brain abnormalities consistent with MS, and no worsening of neurological symptoms within 30 days of screening and baseline. The MS diagnosis was

made using the 2010 revised McDonald criteria. Key exclusion criteria included any previous treatment with a B cell–targeted therapy or other immunosuppressive medication, and a disease duration of more than 10 years in combination with an EDSS score of 2.0 or lower at screening.

## Outcomes

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

- Relapse — defined in the OPERA-I and OPERA-II trials as new or worsening neurological symptoms with the following criteria: attributable to MS only in the absence of fever or infection; persistent for more than 24 hours; immediately preceded by a stable or improving neurological state for at least 30 days; and accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS, two points in one EDSS functional system score, or one point in each of two or more EDSS functional system scores. All new or worsening neurological events consistent with a clinical relapse were documented on a dedicated page of the case report form. Patients with clinical relapses were subsequently referred to the examining investigator, who conducted an independent assessment of the EDSS to confirm whether the event met these criteria for a relapse.
- Confirmed disability progression (CDP) — 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 lower; or an increase of 0.5 from baseline when the baseline score was higher than 5.5. Disability progression was confirmed when the increase from baseline in EDSS was documented at a regularly scheduled clinic visit at least 12 or 24 weeks after the patient's neurological worsening was initially documented.
- Confirmed disability improvement — defined as a reduction in EDSS score from baseline of at least 1.0 for those with a baseline score between 2 and 5.5, or a reduction of at least 0.5 when the baseline EDSS score was greater than 5.5.
- MRI end points — End points that were evaluated using MRI included the following: change in brain volume from week 24 to week 96; total number of new or newly enlarged hyperintense lesions on T2-weighted scans by week 96; total number of new hypointense lesions by week 96; and total number of new gadolinium-enhanced lesions on T1-weighted scans. MRI scans were scheduled for day 1, week 24, week 48, and week 96.
- Multiple Sclerosis Functional Composite (MSFC) — includes three objective and quantitative continuous scales that assess leg function/ambulation (with timed 25-foot walk), arm/hand function (with the nine-hole peg test), and cognitive function (with the Paced Auditory Serial Addition Test 3). Scores on component measures are converted to standard scores (z scores), which are averaged to form a single MSFC score. A positive change in the composite z score indicates improvement, and a negative change indicates worsening. A 20% change in scores on timed 25-foot walk trials and nine-hole peg tests, and a 0.5 standard deviation change on the Paced Auditory Serial Addition Test 3 are considered clinically meaningful.
- SF-36 — a 36-item generic health-status measure of 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. The eight subdomains are each 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 and the Mental Component Summary.
- No Evidence of Disease Activity (NEDA) — Patients who completed the 96-week treatment period were considered to have evidence of MS disease activity if any of the following were reported during the double-blind study period: at least one protocol-defined relapse; a CDP event; or at least one MRI scan demonstrating gadolinium-enhanced lesions on T1-weighted images or new or enlarging lesions on T2-weighted images. If none of the aforementioned events were reported, the patient was considered to have NEDA.

## Efficacy

- Treatment with ocrelizumab was associated with a statistically significant reduction in ARR compared with interferon beta-1a at 96 weeks in OPERA-I, OPERA-II, and the pooled analysis (rate ratios 0.536 [95% CI, 0.400 to 0.719], 0.532 [95% CI, 0.397 to 0.714], and 0.535 [95% CI, 0.435 to 0.659], respectively). The reduction in the ARR with ocrelizumab was 46% in OPERA-I and 47% in OPERA-II and the pooled analysis.
- A greater proportion of ocrelizumab-treated patients remained free of relapses compared with the interferon beta-1a group in both OPERA-I (80.4% versus 66.7%; relative risk [RR] 1.20 [95% CI, 1.10 to 1.31], $P < 0.0001$) and OPERA-II (78.9% versus 64.3%; RR 1.23 [95% CI, 1.12 to 1.35]; $P < 0.0001$).
- The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant reduction in CDP for both 12-week and 24-week clinic visit (hazard ratio [HR] 0.60 [95% CI, 0.45 to 0.81] and 0.60 [95% CI, 0.43 to 0.84], respectively).
- The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant increase in the proportion of patients with confirmed disability improvement (RR 1.33 [95% CI, 1.05 to 1.68]; $P = 0.0194$].
- Ocrelizumab was associated with a statistically significant reduction in the rate of new or newly enlarged hyperintense lesions on T2-weighted images by week 96, new hypointense lesions by week 96, and new gadolinium-enhanced lesions on

T1-weighted images in both the individual trials and the pooled analysis. There was no statistically significant difference between ocrelizumab and interferon beta-1a for change in brain volume from week 24 to 96 in the OPERA-II trial (mean difference [MD] 0.112 [95% CI, −0.018 to 0.241]; *P* = 0.0900). Failure to demonstrate a statistically significant difference for change in brain volume stopped the statistical testing hierarchy at this end point in OPERA-II. The statistically testing hierarchy in OPERA-I had stopped at a higher-order end point; therefore, the difference favouring ocrelizumab over interferon beta-1a reported by the manufacturer is not considered statistically significant (MD 0.168 [95% CI, 0.053 to 0.283]; *P* = 0.0042).

- In both studies, the mean SF-36 Physical Component Score for patients in the interferon beta-1a group showed a decrease from baseline (−0.833 to −0.657), whereas the mean scores in the ocrelizumab groups showed a slight increase from baseline (0.036 to 0.326). The pooled analysis of the two studies suggested greater improvement in ocrelizumab-treated patients compared with those treated with interferon beta-1a (MD 0.918 [95% CI, 0.135 to 1.702]; *P* = 0.02).
- There was no statistically significant difference between ocrelizumab and interferon beta-1a for change from baseline in the MSFC in OPERA-I (MD 0.039 [95% CI, −0.039 to 0.116; *P* = 0.3261). Failure to demonstrate a statistically significant difference for this end point stopped the statistical testing hierarchy at this end point in OPERA-I. In contrast, statistically significant differences favouring ocrelizumab over interferon beta-1a were observed in the OPERA-II trial (MD 0.107 [95% CI, 0.034 to 0.180]; *P* = 0.0040) and in the pooled analysis (MD 0.077 [95% CI, 0.025 to 0.129]; *P* = 0.004).
- The statistical testing hierarchy had been stopped before the evaluation of NEDA in both OPERA-I and OPERA-II. In both studies, a greater proportion of ocrelizumab-treated patients achieved NEDA at week 96 (43.9% to 47.4%) compared with those treated with interferon beta-1a (24.1% to 27.1%). The relative risks for NEDA were 1.74 (95% CI, 1.39 to 2.17) in OPERA-I and 1.81 (95% CI, 1.41 to 2.32) in OPERA-II.

## Harms (Safety and Tolerability)

- The proportion of ocrelizumab-treated patients who experienced at least one serious adverse event was similar in the OPERA-I and OPERA-II trials (6.9% [39 events] and 7.0% [39 events], respectively). The proportion of patients treated with interferon beta-1a treated who experienced at least one serious adverse event was 7.8% (38 events) in OPERA-I and 9.6% (50 events) in OPERA-II. The most commonly reported classes of serious adverse events across both studies were infections and infestations (1.3% with ocrelizumab and 2.9% with interferon beta-1a); nervous system disorders (1.0% with ocrelizumab and 1.3% with interferon beta-1a); and injury, poisoning, and procedural complications (0.7% with ocrelizumab and 1.2% with interferon beta-1a).
- In both studies, withdrawals as result of adverse events were more frequently reported in the interferon beta-1a groups (6.0% to 6.4%) compared with the ocrelizumab groups (3.2% to 3.8%). Infusion-related reactions led to withdrawal of 11 ocrelizumab-treated patients (1.2% to 1.5%) compared with no patients for those who received the placebo infusion.
- Serious infections were more commonly reported for patients who received treatment with interferon beta-1a (3.8% [34 events]) compared with the ocrelizumab group (1.8% [18 events]). The proportion of patients who experienced at least one adverse event that was classified as an opportunistic infection was greater in the ocrelizumab group (7.0%) compared with the interferon beta-1a group (4.1%). The manufacturer reported that this imbalance was primarily due to an increase in herpesvirus infections in the ocrelizumab groups compared with the interferon groups. These included including oral herpes (2.9% versus 2.1%), herpes zoster (2.1% versus 1.0%), and herpes simplex (0.8% versus 0.2%).
- Infusion-related reactions were the most commonly reported adverse events in both of the pivotal trials, and these occurred at a greater frequency in the ocrelizumab groups compared with the interferon beta-1a groups (34.3% versus 9.7% in the pooled analysis). There were no events of anaphylaxis reported in the OPERA-I or OPERA-II trials. The most commonly reported symptoms associated with infusion-related adverse events in the ocrelizumab groups were pruritus, rash, throat irritation, and flushing. The first 300 mg dose of ocrelizumab was associated with the highest proportion of patients with an infusion-related event (27.5%), which decreased to 4.7% for the second 300 mg infusion. Following the first infusion of the full 600 mg ocrelizumab dose, 13.7% of patients reported at least on infusion-related event. This proportion subsequently decreased for the third and fourth doses (9.6% and 7.8%, respectively).
- Nearly all of the infusion-related adverse events were mild or moderate in severity (93% in the ocrelizumab group and 99% in the interferon beta-1a group were grade 1 or 2 events). Grade 3 infusion-related adverse events were reported 20 ocrelizumab treated patients (2.4%) compared with one (0.1%) patient in the interferon beta-1a group. There was one grade 4 event (bronchospasm) reported for an ocrelizumab-treated patient at the time of the first 300 mg infusion. Eleven ocrelizumab-treated patients withdrew from the study as a result of infusion-related adverse events (1.3%), in all cases after receiving one infusion of ocrelizumab (i.e., 300 mg).
- No cases of progressive multifocal leukoencephalopathy were reported in patients treated with ocrelizumab in the OPERA trials.

## Network Meta-Analyses

Two network meta-analyses (NMAs) were reviewed and critically appraised by CADTH (one unpublished NMA submitted by the manufacturer and one published NMA conducted by the Institute for Clinical and Economic Review). Both NMAs demonstrated that ocrelizumab was associated with a lower ARR than several other disease-modifying therapies, including interferon beta-1a (administered by subcutaneous and intramuscular routes), teriflunomide, glatiramer acetate, peginterferon beta-1a, and dimethyl fumarate. The two NMAs reported that there was no evidence of a difference between patients treated with ocrelizumab and those treated with natalizumab and alemtuzumab for reducing the rate of relapse. The analysis of safety end points in the indirect comparisons was limited to aggregate outcomes (i.e., serious adverse events and all-cause discontinuations), and the results suggested that there were no differences among any of the disease-modifying therapies included in the analyses. However, such aggregate end points cannot be used to evaluate the unique safety profiles of disease-modifying therapies.

## 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; the annual cost of ocrelizumab is $32,600 per patient.

The manufacturer submitted a cost-utility analysis comparing ocrelizumab with currently available treatments for adult patients with RRMS. Comparators included other infusion therapies (alemtuzumab and natalizumab), as well as injectable therapies (interferon beta-1a, interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, and daclizumab) and oral therapies (dimethyl fumarate, fingolimod, and teriflunomide). A Markov cohort model was used to simulate the disease course of patients with relapsing forms of MS receiving ocrelizumab or other relevant comparators, based on progression through EDSS scores. In this model, patients transitioned between EDSS states 0 through 9 in RRMS and in secondary-progressive MS, and could progress from RRMS to secondary-progressive MS; at any point, patients could also transition to the absorbing death state. The analysis was run over a lifetime time horizon (approximately 63 years) using annual cycles and undertaken from the perspective of the Canadian public health care payer.

In its base case, the manufacturer reported pairwise comparisons in which ocrelizumab was more costly and more effective when compared with alemtuzumab, dimethyl fumarate, glatiramer acetate, interferon beta-1a, peginterferon beta-1a, and teriflunomide, resulting in incremental cost-effectiveness ratios ranging from $20,300 to $39,600 per QALY gained. When compared with other comparators (i.e., daclizumab, fingolimod, and natalizumab), ocrelizumab was less costly and associated with greater QALYs. In a sequential analysis considering all comparators, ocrelizumab was more costly and more effective that peginterferon beta-1a, resulting in an incremental cost-effectiveness ratio of $46,121 per QALY gained; all other treatments were either dominated or subject to extended dominance.

CDR identified several limitations with the submitted economic model:

- CDP estimates based on a 12-week confirmation period (CDP-12) may be a poor indicator of permanent disease worsening for a long-term condition. Use of 24-week CDP estimates may be more reflective of clinical outcomes over an annual cycle.
- Treatment efficacy was applied in the economic model for the duration of treatment for all comparators other than alemtuzumab. Treatment with alemtuzumab was assumed to continue for no more than two years. This approach to modelling the duration of treatment and efficacy was biased against alemtuzumab and unsupported by evidence.
- There is uncertainty with estimates from manufacturer-commissioned indirect treatment comparisons due to their reliance on mixed trials of treatment-naive and/or treatment-experienced patients for evidence synthesis, lack of assessment of the impact of clinical heterogeneity, and lack of statistical analysis for inconsistency.
- The submitted model lacked transparency and was unnecessarily complex. This made it challenging to assess validity and to conduct the reanalysis.
- Other parameters of uncertainty included health state utility values (EDSS 8 and 9), treatment cost of daclizumab, and natural history data.

The CDR reanalysis accounted for the identified limitations and found that ocrelizumab was not a cost-effective treatment for adult patients with RRMS when considering all available therapies regardless of a decision-maker's willingness-to-pay threshold for a gain of one QALY. The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 2.0%, and the probability at a threshold of $100,000 was 12.9%. In the CDR base case, peginterferon beta-1a was the optimal therapy at a willingness-to-pay threshold of less than $151,610 per QALY gained, while dazlicumab was the optimal therapy if a decision-maker's willingness to pay for a gain of one QALY was greater than $151,610 but less than $258,857. If a decision-maker's willingness to pay for one QALY was greater than $258,857, alemtuzumab was the optimal therapy. At a price reduction of at least 50% of the submitted price, the probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 81%.

## 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.

## October 18, 2017, Meeting

## Regrets:

None

## Conflicts of Interest:

None