CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

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

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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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Abbreviations

BSC	best supportive care
CDR	CADTH Common Drug Review
EDSS	Expanded Disability Status Scale
MS	multiple sclerosis
PPMS	primary progressive multiple sclerosis
QALY	quality-adjusted life-year
QoL	quality of life
RRMS	relapsing remitting multiple sclerosis

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Ocrelizumab (Ocrevus) 300 mg vial
Study Question	What is the incremental cost-effectiveness of ocrelizumab for the treatment of PPMS compared with BSC in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with PPMS in Canada
Treatment	Ocrelizumab 600 mg IV every 6 months
Outcome(s)	Quality-adjusted life-years
Comparator(s)	BSC (consists of outpatient visits [to physicians, physiotherapists, occupational therapists, nurses, and psychologists], rehabilitation care, hospitalizations, and medication to manage symptoms)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (approximately 56 years)
Results for Base Case	• Ocrelizumab was costlier and more effective (i.e., gained more QALYs) when compared with BSC. The incremental QALY gain was 0.72; the increase in health care costs was $206,977, leading to an incremental cost per QALY gained of $289,333. • The probability that ocrelizumab was cost-effective given a willingness-to-pay threshold of $50,000 per QALY was 0%.
Key Limitations	• Lack of data on costs and mortality specific to PPMS. • Errors in the use of mortality data by EDSS. • Use of alternative utility values for EDSS states 0, 1, 8, and 9, which appeared to lack validity compared with utility values for EDSS states 2 to 7. Utility values for these states were available from the ORATORIO study. • The assumption of improving health status was not supported by the clinical expert consulted by CADTH. • The analysis excluded the increased risk of cancer with ocrelizumab.
CDR Estimate(s)	CDR reanalysis of the manufacturer's base case addressed the issues relating to mortality, utility values, and improving health status. The CDR base case found an incremental QALY gain of 0.33 and incremental health care costs of $193,839, leading to an incremental cost per QALY gained of $588,148. The probability that ocrelizumab was cost-effective given a willingness-to-pay threshold of $50,000 per QALY was 0%. Further analysis incorporating the effects of the potential increase in cancer with ocrelizumab on mortality found ocrelizumab to be costlier and less effective than BSC.

BSC = best supportive care; CDR = CADTH Common Drug Review; EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; QALY = quality-adjusted life-year.

Drug	Ocrelizumab (Ocrevus)
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
Reimbursement Request	As per indication.
Dosage Form(s)	300 mg vial
NOC Date	February 14, 2018
Manufacturer	Hoffmann-La Roche Limited

Executive Summary

Background

Ocrelizumab (Ocrevus) is a recombinant humanized monoclonal antibody that selectively targets and depletes CD20-expressing B-cells, which are thought to contribute to the inflammatory and neurodegenerative pathogenesis of multiple sclerosis (MS). Ocrelizumab is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS),[1] and was previously reviewed by CADTH. The CADTH Canadian Drug Expert Committee recommended that ocrelizumab be listed for RRMS based on the condition of a price reduction of at least 50%.[2] This submission relates to an application to Health Canada for an indication relating to the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.[3]

Ocrelizumab is available in 300 mg single-use vials for infusion. It is recommended that an initial 600 mg dose be administered as two separate IV infusions (an initial 300 mg infusion followed by a second 300 mg infusion two weeks later), with subsequent ocrelizumab doses administered as single 600 mg IV infusions every six months.[1] At a manufacturer-submitted unit price of $8,150 per 300 mg vial, ocrelizumab costs $32,600 per patient per year.[3] The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing ocrelizumab with best supportive care (BSC). BSC includes outpatient visits, rehabilitation, hospitalization, and medication for symptom management. BSC was chosen as the sole comparator as there are no licensed pharmacological treatments for PPMS in Canada.[4] In the model, PPMS patients transitioned through Expanded Disability Status Scale (EDSS) states 0 to 9.[5] In each cycle, patients can transition to the death state, with the probability of death varying by disease severity. The analysis was run over a lifetime time horizon (up to an age of 100 years) using an annual cycle length. The analysis adopted a Canadian public health care system perspective.

Data on natural history were derived from the MSBase data set.[6] The effect of ocrelizumab on natural history was derived from the ORATORIO clinical trial.[7] Treatment was assumed to stop once patients reached EDSS 7. The increase in mortality by EDSS for modelled PPMS patients was assumed to be the same as for RRMS and used data from a previous study.[8] Adverse events with ocrelizumab were included in terms of their effect on cost and utility values (infusion-related reactions, nasopharyngitis, urinary tract infections). Costs by

EDSS state were based on costs from a Canadian report for RRMS.[9,10] Utility values for EDSS states 2 to 7 were derived from the ORATORIO study;[11] for EDSS states 0,1, 8, and 9, data from the Orme et al.[12] study relating to RRMS was used.

The manufacturer reported that ocrelizumab was costlier and more effective than BSC. The incremental quality-adjusted life-year (QALY) gain was 0.72 and the increase in health care costs was $206,957, leading to an incremental cost per QALY gained of $285,471. The probability that ocrelizumab was cost-effective given a willingness-to-pay threshold of $50,000 per QALY was 0%.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified a number of key limitations relating to the manufacturer's economic model.

Data for mortality were derived from a report by Pokorski et al.[8] of a study by Sadovnick et al.[13] that was not specific to patients with PPMS, and likely included predominantly RRMS patients. The study provided excess mortality calculations for mild, moderate, and severe MS patients, from which mortality multipliers were obtained by EDSS score. There are concerns over how these mortality multipliers were derived and incorporated into the model. As well, the nature of the data was problematic: the patient population (likely reflective of RRMS), the characterization of disease severity, and the lack of relevance to current management (data from 1972 to 1985) all raise concerns regarding the relevance of the data to the current Canadian PPMS patient population.

The natural history of patients (how patients transition in the model) was derived from the MSBase data set.[6] Based on information, patients could experience an improvement in EDSS state; for some states, the probability of improvement exceeded 10%. The clinical expert consulted by CADTH for this review did not accept that this was likely given the nature of the condition. Reanalysis excluded the probability of health status improvement.

Utility values for EDSS states 2 to 7 were derived from the ORATORIO data set and ranged from 0.80 to 0.55.[11] Utility values for EDSS 0,1, 8, and 9 were derived from a previous study in RRMS patients by Orme et al.[12] The manufacturer assumed utility values for EDSS 8 and 9 of less than 0 (–0.082 and –0.228, respectively). These values lack face validity given that the utility value for EDSS 7 was 0.55. As such, CDR requested further utility data from ORATORIO. The manufacturer submitted information for utility values for EDSS states 1 to 8.5,[11] which was used in the CDR reanalysis. In addition, CDR wished to verify any utility benefit from ocrelizumab and asked the manufacturer to provide data from the ORATORIO study relating to utility data by study arm derived from the Short Form Six-Dimension (SF-6D) utility instrument for each time point (i.e., baseline up to 96 weeks). The manufacturer did not provide this data to CDR.

The CDR reanalysis incorporated mortality multipliers based on the original study, the assumption of no improvement in health status over time, and utility data from the ORATORIO data set. CDR found that ocrelizumab led to an increase in QALYs of 0.33 and an increase in costs of $193,839, resulting in an incremental cost per QALY gained of $588,148.

Conclusions

CDR found that ocrelizumab was not a cost-effective treatment for adult patients with PPMS, with an incremental cost per QALY gained of $588,143. Ocrelizumab had a 0% probability of being cost-effective at willingness-to-pay thresholds up to $200,000 per QALY. CDR reanalysis suggests that a reduction of 80% in the submitted price would lead to an incremental cost per QALY of $68,378.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted an economic model that captured health outcomes in terms of quality-adjusted life-years (QALYs) gained. The model compared the cost-effectiveness of ocrelizumab with best supportive care (BSC) in the management of patients with primary progressive multiple sclerosis (PPMS).[4] The target population was based on the population within the ORATORIO trial, with an average age of 44 years and a distribution across Expanded Disability Status Scale (EDSS) states 3 to 7.[7] The analytical time horizon was 56 years (concluding at age 100). The analysis incorporated a discount rate of 1.5% per annum and was conducted from the perspective of the Canadian publicly funded health care system.

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of PPMS patients receiving treatment with ocrelizumab and those receiving BSC. The model was based on patients transitioning through EDSS states 0 to 9 and death.[5] The model adopted a cycle length of one year. Patients with PPMS entered the model in a state between EDSS 3 and 7.

In each cycle, patients could transition between EDSS states or enter the absorbing death state. It was assumed that patients who reached an EDSS score of 7 or greater while on treatment with ocrelizumab would discontinue treatment. Following discontinuation, patients switched to "untreated" EDSS states, with transitions informed by natural history data. The probability of death from EDSS states was based on general population mortality adjusted by EDSS state-specific mortality multipliers.[10]

Model Inputs

For patients on BSC, transition probabilities between EDSS states were derived from natural history information relating to untreated PPMS from the MSBase study.[6] For patients receiving ocrelizumab treatment, the natural history data were adjusted by a treatment effect derived from the ORATORIO study.[7] After discontinuing treatment with ocrelizumab, patients were assumed to experience the same transition probabilities as those on BSC.

The probability of mortality was based on adjusting all-cause mortality data for the Canadian general population by EDSS state-specific mortality multipliers. These multipliers are derived from a report by Pokorski et al.[8] utilizing data from a study by Sadovnick et al.[13]

Health state utilities in the model were based on disease severity (as measured by EDSS). For EDSS 2 to 7, utility values from the ORATORIO study specific to PPMS were adopted.[11] For EDSS 0,1, 8, and 9, utility values for EDSS states were taken from a study by Orme et al.[12]

Costs for patient management by EDSS state were derived from a previous study used within the recent CADTH therapeutic review, adjusted to 2017 Canadian dollars.[9,10]

Manufacturer's Base Case

The manufacturer reported that the costs associated with ocrelizumab and BSC were $744,217 and $537,260 respectively, leading to an incremental cost of $206,957. Total QALYs were 12.49 and 11.76 for ocrelizumab and BSC, respectively, leading to an incremental QALY gain of 0.72 (Table 2). The estimated incremental cost per QALY gained was $285,471.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incr. Cost Versus BSC ($)	Total QALYs	Incr. QALYs Versus BSC	Incremental Cost ($) per QALY Gained : Ocrelizumab Versus BSC
BSC	537,260	–	11.76	–	–
Ocrelizumab	744,217	206,957	12.49	0.72	285,471

BSC = best supportive care; Incr. = incremental; QALY = quality-adjusted life-year.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs and QALYs are probabilistic values, based on a revised economic model submitted to CADTH on December 5, 2017.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a range of probabilistic scenario analyses. Analysis considered alternative assumptions relating to time horizon (three months and eight years), discount rate (0% and 3% per annum), perspective (societal), utility values (Orme et al. for all values[12]), natural history data (ORATORIO), effect duration (for three years only, and reduced effect after three years), and mortality multiplier (increased mortality with PPMS).

All analyses lead to the same conclusion, with ocrelizumab being costlier and more effective. The incremental cost per QALY gained ranged from $234,636 to $4.0 million.

Limitations of Manufacturer's Submission

CADTH Common Drug Review (CDR) identified the following limitations with the manufacturer's model.

Choice and handling of mortality data: Data for mortality were derived from a report by Pokorski et al.[8] utilizing data from a study by Sadovnick et al.[13] that was not explicit to PPMS and likely focused predominantly on relapsing remitting multiple sclerosis (RRMS) patients. The study provided excess mortality calculations for mild, moderate, and severe multiple sclerosis (MS) patients. From this, mortality multipliers were obtained by EDSS score. There are concerns over how these mortality multipliers were derived and the uncertainty around these incorporated into the model.

The likely population was predominantly RRMS patients. Thus, it is unclear if mortality by EDSS would vary significantly between RRMS and PPMS patients. A larger concern is the temporal nature of the data, in that the data relates to the period 1972 to 1985. Changes in symptom management over time may lead to questions regarding the relevance of the data, which relates to a period where the care of MS patients may have been significantly different. Finally, there are concerns over how the data were analyzed. The original data for Sadovnick et al. suggest a mortality multiplier of 1.6 for EDSS scores between 0 and 3.5,

1.84 for EDSS scores between 4 and 7, and 4.45 for EDSS scores of 7.5 or greater.[13] The submission assumes that the values relate to the following categories: EDSS from 1 to 3, EDSS from 4 to 6, and EDSS from 7 to 9.[4] Thus, these do not completely match the original data. Furthermore, the submission includes an assumption whereby mortality multipliers for individual EDSS states are derived based on a predictive function that the manufacturer states is based on the analysis by Sadovnick et al.[4] The original Sadovnick et al. article states that such analysis was not done due to the limited number of cases analyzed.[13] Thus, it is unclear how such data were derived. CDR adopted an approach whereby the multipliers by EDSS category were used as reported in the original article by Sadovnick et al.[13] The final concern with the handling of the mortality multiplier is in the specification of uncertainty whereby the distribution for each multiplier is curtailed by enforcing a minimum value of 1; this will artificially increase the effect of the multiplier and result in overestimating the gains form ocrelizumab. CDR applied the data from the Sadovnick et al. article to specify the uncertainty around the multipliers.[13]

Assumed improvement in health status: Transition probabilities relating to natural history were derived from the MSBase data set.[6] The model allowed for an improvement in EDSS state within a cycle (Figure 2). For some states, the probability of improvement exceeded 10% (e.g., the probability of patients in EDSS state 5 moving to EDSS state 1 to 4 in the next cycle was 20%). The clinical expert consulted by CADTH for this review did not feel this was reflective of the natural history of MS. Reanalysis excluded the probability of health status improvement. This was implemented by assuming that all patients who were assumed to improve in the original model would remain in their current states (Figure 3). For example, for EDSS state 5, 20% were assumed to improve and 39% were assumed to remain in EDSS 5. In the CDR revised analysis, 59% remained in EDSS state 5.

Utility values: Utility values for EDSS states 2 to 7 were derived from the ORATORIO data set and ranged from 0.80 to 0.55.[11] Utility values for EDSS 0,1,8, and 9 were derived from a previous study in RRMS patients by Orme et al.[12] Therefore, the manufacturer assumed utility values for EDSS 8 and 9 of –0.082 and –0.228 (Figure 4).These values lacked face validity given the utility value for EDSS 7 of 0.55; i.e., the transition from EDSS 7 to 8 leads to a utility decrease of 0.63. The utility decrease by EDSS for states 2 to 7 ranged from 0.01 to 0.13.

To ensure that utility values had face validity, CDR requested further utility data from ORATORIO. The manufacturer provided a poster presented at an ISPOR conference for the Daigl et al. study. It provided estimates for utility values for EDSS states from 1 to 8.5.[11] These were then used in the CDR reanalysis (Figure 5). Given that patients entered the model in EDSS state 3 or higher, and no improvement in health status was allowed in the CDR analysis, the assumptions around the utility values for EDSS states 0 and 1 did not affect the final results. CDR attempted to verify any utility benefit from ocrelizumab, and requested that the manufacturer provide data from the ORATORIO study relating to utility values by study arm derived from the Short Form Six-Dimension (SF-6D) utility instrument for each time point (i.e., baseline to 96 weeks). However, the manufacturer chose not to provide this data.

Impact on cancer prevalence: Within the ORATORIO study, higher rates of neoplasms were observed in the ocrelizumab versus the BSC group: 2.3% versus 0.8%.[7] Experience across all ocrelizumab trials found a neoplasm rate of 0.40 per 100 patient-years of exposure for ocrelizumab compared with 0.20 per 100 patient-years of exposure in comparator arms. CDR attempted a tentative analysis by including the increased probability

of neoplasm for patients receiving ocrelizumab (0.2% per annum) and by using the current estimate of the case fatality rate for cancer in Canada – 40% according to the Canadian Cancer Society.[14] No additional costs or disutilities from cancer were incorporated; as a result, this analysis may be seen as an underestimate of the impact of the increased probability of cancer associated with ocrelizumab on its cost-effectiveness.

Use of cost data for RRMS: The manufacturer's analysis employed cost data by EDSS state, which were derived from a Canadian study of 153 patients with RRMS and adjusted by CADTH to allow estimation of costs for all EDSS states.[9,10] It would have been preferable to employ cost estimates for PPMS; but the likely impact on the conclusions of the study with respect to cost-effectiveness may be minimal, given that ocrelizumab was not cost-effective in ether the manufacturer's or CDR's analysis.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several important shortcomings relating to the manufacturer's model. CDR presents a revised probabilistic analysis (CDR base case) in Table 3 with alternations based on these limitations. The modifications made to the manufacturer-submitted model include:

- Adoption of the original mortality multipliers form the Sadovnick et al. article[13]
- No assumption of improvements in EDSS state
- Use of utility values for all EDSS states from the ORATORIO study.[11]

In addition, a further reanalysis (Table 4) incorporated a 0.2% increase in the annual probability of cancer per annum with treatment with ocrelizumab and an associated probability of death of 40%.[14]

Based on these revisions, the CDR base case (Table 3) suggests that ocrelizumab is not a cost-effective treatment for patients with PPMS unless decision-makers have a very high willingness to pay for a QALY gained in this patient population. The incremental cost per QALY gained for ocrelizumab versus BSC was estimated to be $588,148, with the probability that ocrelizumab is cost-effective being 0% for all QALY values up to $200,000. Thus, if a decision-maker is unwilling to pay $588,148 for each QALY gained, BSC is the optimal therapy. If a decision-maker is willing to pay at least $588,148 for each QALY gained, ocrelizumab is the optimal therapy.

Table 3: CADTH Common Drug Review Base Case

	Total Costs ($)	Incr. Cost Versus BSC ($)	Total QALYs	Incr. QALYs Versus BSC	Incremental Cost ($) per QALY Gained: Ocrelizumab Versus BSC
BSC	669,909	-	14.12	-	-
Ocrelizumab	863,748	193,039	14.45	0.33	588,148

BSC = best supportive care; Incr. = incremental; QALY = quality-adjusted life-year.

When the increased probability of cancer with ocrelizumab was considered, the CDR analysis found ocrelizumab to be dominated by BSC, with higher associated costs and lower QALYs (Table 4). Thus, in this analysis, ocrelizumab was not the optimal therapy regardless of a decision-maker's willingness to pay for a QALY gained. The probability that ocrelizumab is cost-effective was 0% for all values of a QALY up to $285,000.

Table 4: CADTH Common Drug Review Base Case With the Addition of the Increased Probability of Cancer With Ocrelizumab

	Total Costs ($)	Incr. Cost Versus BSC ($)	Total QALYs	Incr. QALYs Versus BSC	Incremental Cost ($) per QALY Gained: Ocrelizumab Versus BSC
BSC	671,065	-	14.08	-	-
Ocrelizumab	839,865	168,800	14.02	–0.06	Ocrelizumab dominated by BSC

BSC = best supportive care; Incr. = incremental; QALY = quality-adjusted life-year.

CDR undertook a price reduction analysis based on the manufacturer-submitted and CDR base-case analyses assuming proportional price reductions for ocrelizumab (Table 5).

Using the manufacturer's base-case analysis, a price reduction of 71% for ocrelizumab was required for ocrelizumab to be cost-effective based on a threshold of $50,000 per QALY. The CDR base-case analysis suggested that ocrelizumab would be cost-effective based on a threshold of $50,000 per QALY if an 82% price reduction were obtained.

Table 5: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

Incremental Cost per QALY Gained for Ocrelizumab Versus BSC		
Price	**Based on Manufacturer's Base Case**	**Based on CDR Base Case**
Submitted	$289,333	$588,143
10% reduction	$255,972	$523,172
20% reduction	$222,611	$458,201
30% reduction	$189,251	$393,231
40% reduction	$155,890	$328,260
50% reduction	$122,529	$263,290
60% reduction	$89,168	$198,319
70% reduction	$55,807	$133,348
80% reduction	$22,447	$68,378
90% reduction	Ocrelizumab dominates BSC	$3,407

BSC = best supportive care; CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

Patient Input

Patient input was received from the Multiple Sclerosis Society of Canada (MS Society). One hundred and eighty-six patients diagnosed with PPMS responded to an online questionnaire issued by the MS Society; patients noted that unlike relapsing forms of MS, PPMS is characterized by continuous worsening of disease. This contrary to the data within the manufacturer's model and supports CDR's reanalysis based on the progressive nature of the disease. The worsening of disease often results in the need for wheelchair assistance as a result of reduced mobility due to significant neurological disability. According to the survey respondents, PPMS is also associated with a wide range of symptoms, including fatigue, cognitive impairment, weakness, spasticity, tremor, poor coordination, bladder and bowel problems, sexual dysfunction, depression, pain, dizziness, visual problems, and issues with speech and swallowing. Given that PPMS is typically diagnosed after the age of 40, it exerts a significant impact on many aspects of a patient's life, including quality of life (QoL), psychosocial functioning, and the ability to maintain employment and participate in activities of daily living. The impact of this condition on a patient's QoL was accounted for in the

manufacturer's economic evaluation by including progressively lower utilities with increasing level of disease severity (i.e., increasing EDSS level). Patients living with PPMS emphasized that an increasing loss of physical strength was associated with their condition, significantly affecting their ability to live independently and interact with the outside world; as a result of decreased motor function, reliance on caregiver support is high. Caregiver burden was not accounted for in the manufacturer's base-case analysis. While this was considered in a scenario analysis, only the cost of lost productivity and information caregiving was included, and not the impact on caregivers' QoL.

Conclusions

CDR found that ocrelizumab was not a cost-effective treatment for adult patients with PPMS, given the incremental cost per QALY gained of $588,143 (when excluding the additional effects of increased cancer prevalence with ocrelizumab). Ocrelizumab had a 0% probability of being cost-effective at willingness-to-pay thresholds up to $200,000 per QALY. CDR reanalysis suggests that a reduction of 80% in the submitted price would lead to an incremental cost per QALY of $68,378.

It should be noted that the CDR base case did not include the increased probability of cancer with ocrelizumab. If that were included, then ocrelizumab would be dominated by BSC: that is, ocrelizumab would be costlier and less effective than BSC.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and as such, may not represent the actual costs to public drug plans.

Table 6: CADTH Common Drug Review Cost Comparison Table for the Treatment of Primary Progressive Multiple Sclerosis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Ocrelizumab (Ocrevus)	300 mg/10 mL solution for infusion	Single-use vial	8,150.00[a]	600 mg IV every six months[b]	627	32,600

[a] Manufacturer-submitted price.[3]

[b] The initial 600 mg dose is administered as two separate IV infusions: an initial 300 mg infusion followed two weeks later by a second 300 mg infusion. Subsequent doses are administered as single 600 mg IV infusions every six months.[1]

Appendix 2: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”			
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”			
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”			

Table 8: Authors’ Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

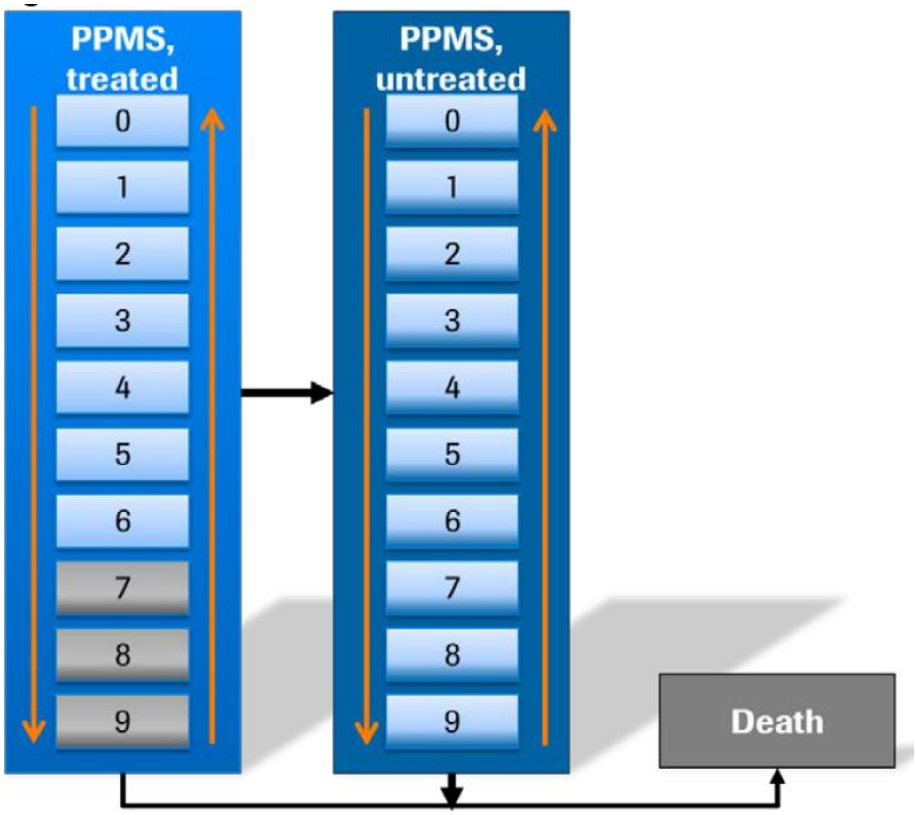
Note that there are no reviews for ocrelizumab in PPMS conducted by Health Technology Assessment organizations available at the time of this review. Ocrelizumab is currently undergoing review at the National Institute for Health and Care Excellence in the UK, the Pharmaceutical Benefits Advisory Committee in Australia, the Pharmaceutical Management Agency in New Zealand, and the Institut national d'excellence en santé et en services sociaux in Quebec.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cohort-based Markov health state-transition model that included 11 health states: 10 Expanded Disability Status Scale (EDSS) states and a death state. The multiple sclerosis (MS)-specific health states were grouped according to the Kurtzke EDSS levels, from 0 (normal neurological examination) to 9 (helpless bed patient).[5] The manufacturer's model structure is presented in Figure 1.

Figure 1: Manufacturer's Model Structure



EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis.

Note: Orange arrows show the direction in which patients may move along the EDSS scale. Grey boxes in "PPMS treated" indicate the stages at which treatment is discontinued.

Source: Manufacturer's pharmacoeconomic submission.[4]

In the submitted model, all patients begin in a PPMS state characterized by EDSS (level 3 = 26.8%; level 4 = 27.4%; level 5 = 15.7%; level 6 = 30.0%; level 7 = 0.14%). The model allows transitions between EDSS states based on data from the MSBase study and incorporates increased risk of death.

Table 9: Data Sources

Data Input	Description of Data Source	Comment
Efficacy, Safety, and Withdrawals		
Efficacy (Disability progression: CDP 12, CDP 24)	The effect of treatment on delaying disability progression (as measured by CDP at 12 and 24 weeks) was derived from the ORATORIO study, a multinational, randomized, double-blind, placebo-controlled clinical trial.[7] ORATORIO compared the efficacy and safety of ocrelizumab with placebo in patients with PPMS.	Appropriate.
Adverse Events	The following AEs were considered: infusion-related reaction, nasopharyngitis, urinary tract infection. The set of AEs considered were those that occurred at an annualized risk of occurrence ≥ 5% for ocrelizumab in the ORATORIO trial. No AEs were associated with BSC, as this comparator did not include additional therapy.	Appropriate.
Treatment Discontinuation (Stopping rule, all-cause discontinuation)	Ocrelizumab was associated with an annual probability of discontinuation, sourced from the ORATORIO trial and applied equally to cost and efficacy parameters. Modelled patients also discontinued therapy upon transitioning to EDSS 7 (stopping rule).	Acceptable.
Natural History		
PPMS to PPMS EDSS Transitions	Transition probabilities between EDSS states (disability progression) in "PPMS, untreated" were estimated based on natural history data for patients not on therapy sourced from the MSBase data set,[6] a global, longitudinal observational registry containing 1,079 patients (8,401 EDSS observations) diagnosed with PPMS. Transition probabilities between EDSS states in "PPMS, treated" were informed by the MSBase data set adjusted by a treatment effect.	While the MSBase data set is a standard, widely used source of natural history data for patients diagnosed with PPMS, and although it may be a better alternative to ORATORIO placebo arm data, information sourced from the MSBase data set is not publicly available; therefore, it was not possible to verify these calculations. Improvement in health status, as observed by backward transitions (i.e., spontaneous remission) within the MSBase data set, was not supported by the clinical expert consulted by CADTH.
Mortality	Transition to death was informed by a weighted mean of all-cause mortality rates for the Canadian general population based on female-to-male ratio of PPMS patients used in the model. Mortality multipliers by MS disease severity (EDSS state) were sourced from Pokorski et al.[8] and applied to the all-cause weighted mean mortality rates.	The values used by Pokorski et al.[8] were derived from a study by Sadovnick et al.[13] that presented mortality rates based on grouped EDSS categories. CDR notes that it would have been better to use actual data than interpolated values. The data are also quite outdated and largely based on RRMS patients; more recent data on mortality by EDSS levels specific to PPMS would be preferred.
Utilities		
Health State Utilities	Utilities were estimated from the ORATORIO trial data using the EQ-5D-3L instrument and based on EDSS state (health states). The Canadian value set for the EQ-5D-3L was used to elicit utility values from the recorded trial data for EDSS 2 to 7.Utility values for	While the utility values derived from trial data may be acceptable, utility values for EDSS states 0, 1, 8, and 9 lacked face validity compared with utility values for EDSS states 2 to 7.

Data Input	Description of Data Source	Comment
	EDSS states 0, 1, 8, and 9 were taken from a study by Orme et al.[12]	
Resource Use and Costs		
Drug	The drug cost for ocrelizumab was provided by the manufacturer. No medications were considered in the BSC arm, as no other medications are licensed for the treatment of PPMS in Canada.	CDR notes no differences between the manufacturer's and CDR's estimate of the yearly acquisition cost of ocrelizumab. Dispensing fees and mark-ups were not included in the submitted model, which is appropriate.
Monitoring	Health care resources associated with monitoring due to ocrelizumab were estimated through clinical expert elicitation (i.e., three clinical advisors consulted by the manufacturer). Unit costs of monitoring resources were obtained from the Ontario Schedule of Benefits. No additional monitoring required for BSC beyond that already associated with EDSS states was assumed.	Appropriate.
Disease Management (Non–drug-related direct health care costs)	Annual per-patient direct costs of PPMS management by EDSS scores were based on values reported in the CADTH MS Therapeutic Review,[10] as well as a study by Grima et al.[9] inflated to 2017 values.	CDR notes that while Canadian data sources were used to inform the cost of disease management, PPMS-specific costs would be preferred.
Adverse Events	Unit costs of physician services required to treat non-serious and serious AEs were obtained from the Ontario Schedule of Benefits.	Appropriate.

AE = adverse event; BSC = best supportive care; CDP = confirmed disability progression; CDR = CADTH Common Drug Review; EDSS = expanded disability status scale; EQ-5D-3L = EuroQol 5-Dimentions 3-Levels questionnaire; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = remitting forms of multiple sclerosis.

Table 10: Manufacturer's Key Assumptions

Assumption	Comment
Patients either progress to a higher EDSS state, remain in the same state, regress to a lower severity EDSS state, or die.	The clinical expert consulted by CADTH for this review indicated that regression to lower EDSS states (i.e., spontaneous remission) in patients diagnosed with PPMS is not very likely. Therefore, progression-only transitions are preferred in natural history modelling for PPMS patients.
Relapses were not included in the model structure.	Appropriate, as only a small proportion of patients experienced relapses in the ORATORIO trial, and the impact of ocrelizumab on relapses was not measured.
Model did not include transitions to EDSS state 10 (i.e., MS-related death).	Appropriate. Patients experience an age-related risk of mortality adjusted for the probability of MS-related death.
A half-cycle correction was applied to all comparators in the model.	Appropriate.
BSC consisted of outpatient visits (to physicians, physiotherapists, occupational therapists, nurses, and psychologists), rehabilitation care, hospitalization, and medication to manage symptoms.	Appropriate, as there are no licensed treatments in Canada for PPMS.
Mortality multipliers by EDSS derived from data on primarily RRMS patients were assumed to apply equally to patients with PPMS.	Uncertain.
Progression of disability was measured using 24-week CDP estimates (i.e., 6-month sustained	Appropriate.

Assumption	Comment
accumulation of disability) and assumed to be appropriate for a 1-year cycle.	
Full efficacy was assumed to be applied for the duration of treatment with ocrelizumab.	Acceptable.
No waning effect of treatment with ocrelizumab was assumed in the base case.	Likely appropriate, as loss of efficacy is generally attributed to progression of illness rather than gradual loss of the effect of ocrelizumab.
The model assumed a stopping rule (treatment discontinuation) at EDSS 7.	Uncertain. This was based on stopping rules for disease-modifying therapies for RRMS in Quebec. As this is the first available pharmacotherapy for PPMS, it is unclear whether this will apply.
Treatment discontinuation prior to the stopping rule (EDSS 7) was assumed based on the all-cause discontinuation rate from ocrelizumab observed in the ORATORIO study.	CDR notes that treatment discontinuation observed in the ORATORIO clinical trial may not accurately reflect the real-world rate of discontinuation from ocrelizumab in PPMS patients.
Resource use and costs sourced from data sources relating to RRMS patients were assumed to apply equally to patients with PPMS.	Uncertain.

Additional Information on Limitations

Natural History Transition Probabilities

Figure 2: Transition Probabilities – Manufacturer's Submission

Disease stage in cycle X	Disease stage in cycle X + 1									
	0	1	2	3	4	5	6	7	8	9
0	0.407	0.293	0.224	0.061	0.013	0.002	0.000	0.000	0.000	0.000
1	0.084	0.262	0.420	0.174	0.051	0.008	0.001	0.000	0.000	0.000
2	0.014	0.090	0.441	0.300	0.126	0.024	0.005	0.000	0.000	0.000
3	0.002	0.016	0.132	0.401	0.333	0.091	0.025	0.001	0.000	0.000
4	0.000	0.002	0.018	0.109	0.518	0.243	0.105	0.005	0.000	0.000
5	0.000	0.000	0.002	0.021	0.172	0.392	0.381	0.030	0.002	0.000
6	0.000	0.000	0.000	0.001	0.013	0.065	0.801	0.110	0.009	0.000
7	0.000	0.000	0.000	0.000	0.001	0.004	0.081	0.777	0.134	0.004
8	0.000	0.000	0.000	0.000	0.000	0.000	0.004	0.082	0.860	0.054
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.096	0.900

Note: Red cells denote the probability of improvement in EDSS.
Source: Manufacturer's pharmacoeconomic submission.[4]

Figure 3: Transition Probabilities – CADTH Common Drug Review Base Case

Disease stage in cycle X	Disease stage in cycle X + 1									
	0	1	2	3	4	5	6	7	8	9
0	0.407	0.293	0.224	0.061	0.013	0.002	0.000	0.000	0.000	0.000
1	0.000	0.346	0.420	0.174	0.051	0.008	0.001	0.000	0.000	0.000
2	0.000	0.000	0.545	0.300	0.126	0.024	0.005	0.000	0.000	0.000
3	0.000	0.000	0.000	0.551	0.333	0.091	0.025	0.001	0.000	0.000
4	0.000	0.000	0.000	0.000	0.647	0.243	0.105	0.005	0.000	0.000
5	0.000	0.000	0.000	0.000	0.000	0.588	0.381	0.030	0.002	0.000
6	0.000	0.000	0.000	0.000	0.000	0.000	0.880	0.110	0.009	0.000
7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.862	0.134	0.004
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.946	0.054
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

Source: Adapted from the manufacturer's pharmacoeconomic submission.[4]

Utility Values

Figure 4: Utility Data From the Manufacturer's Submission

EDSS State	ORATORIO Trial Data (reference case)		Orme[113]	
	Utility Estimate	SE	Utility Estimate*	SE
0	Assumed same as Orme[113]		0.837	0.0449
1			0.766	0.0480
2	0.7993	0.0166	0.672	0.0477
3	0.7630	0.0087	0.5410	0.0518
4	0.7250	0.0090	0.577	0.0477
5	0.7191	0.0118	0.485	0.047
6	0.6789	0.0089	0.427	0.0475
7	0.5498	0.0256	0.264	0.0492
8	Assumed same as Orme[113]		-0.082	0.0503
9			-0.228	0.0742

EDSS = Expanded Disability Status Scale; SE = standard error.

Source: Manufacturer's pharmacoeconomic submission.[4]

Figure 5: Utility Data From the Manufacturer's Conference Presentation

	Assessments/ patients	Impact on utility (95% CI)									
		Australia[8]	Belgium[9]	Canada[10]	France[11]	Italy[12]	Netherlands[13]	Portugal[14]	Sweden[15]	UK[16]	USA[17]
EDSS 1.5 (1–2.5)[a,b]	71/51	0.78 (0.74, 0.82)	0.74 (0.70, 0.78)	0.80 (0.77, 0.83)	0.73 (0.68, 0.78)	0.88 (0.85, 0.91)	0.82 (0.78, 0.87)	0.64 (0.60, 0.68)	0.84 (0.82, 0.86)	0.79 (0.74, 0.84)	0.83 (0.80, 0.87)
EDSS 3 (3–3.5)[b]	381/230	0.73 (0.71, 0.75)	0.69 (0.67, 0.71)	0.76 (0.75, 0.78)	0.67 (0.65, 0.70)	0.86 (0.84, 0.87)	0.78 (0.75, 0.80)	0.59 (0.57, 0.61)	0.82 (0.81, 0.83)	0.74 (0.71, 0.77)	0.80 (0.78, 0.82)
EDSS 4 (4–4.5)[b]	385/231	0.68 (0.66, 0.71)	0.63 (0.61, 0.66)	0.73 (0.71, 0.74)	0.59 (0.56, 0.62)	0.82 (0.81, 0.84)	0.73 (0.70, 0.75)	0.52 (0.50, 0.55)	0.79 (0.78, 0.80)	0.68 (0.65, 0.71)	0.75 (0.74, 0.77)
EDSS 5 (5–5.5)[c]	173/129	0.68 (0.65, 0.70)	0.62 (0.59, 0.65)	0.72 (0.70, 0.74)	0.55 (0.51, 0.59)	0.82 (0.80, 0.84)	0.72 (0.69, 0.76)	0.49 (0.46, 0.52)	0.78 (0.76, 0.79)	0.66 (0.63, 0.70)	0.74 (0.72, 0.77)
EDSS 6 (6–6.5)[c]	525/283	0.63 (0.61, 0.65)	0.58 (0.55, 0.60)	0.68 (0.66, 0.70)	0.49 (0.46, 0.51)	0.78 (0.76, 0.80)	0.67 (0.64, 0.70)	0.44 (0.42, 0.46)	0.76 (0.75, 0.77)	0.60 (0.58, 0.63)	0.70 (0.68, 0.72)
EDSS 7.5 (7–8.5)[c,d]	31/26	0.48 (0.42, 0.54)	0.45 (0.38, 0.51)	0.55 (0.50, 0.60)	0.31 (0.23, 0.39)	0.60 (0.55, 0.65)	0.54 (0.46, 0.61)	0.27 (0.20, 0.33)	0.71 (0.68, 0.74)	0.43 (0.35, 0.51)	0.57 (0.51, 0.62)

CI = confidence interval; EDSS = Expanded Disability Status Scale.

Source: Additional information provided by the manufacturer.[11]

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