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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

OZANIMOD (ZEPOSIA — CELGENE INC., A BRISTOL MYERS SQUIBB COMPANY)
Indication: Multiple sclerosis, relapsing-remitting

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ozanimod should not be reimbursed for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) to decrease the frequency of clinical exacerbations.

Version: 1.0
Publication Date: June 2021
Report Length: 9 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Reasons for the Recommendation

1. Two randomized, double-blind, active comparator-controlled trials (RADIANCE Part B and SUNBEAM) demonstrated that ozanimod 1 mg was superior to interferon beta1a in terms of reducing the annualized relapse rate (ARR). This was based on a relative ARR reduction of 38% (95% confidence interval [CI], 23% to 49%; P < 0.0001) in the RADIANCE Part B study and a relative ARR reduction of 48% (95% CI, 34% to 60%; P < 0.0001) in the SUNBEAM study. However, the pooled analyses of the RADIANCE Part B and SUNBEAM studies for time to onset of disability progression (defined as a sustained worsening in Expanded Disability Status Scale [EDSS] of at least 1-point increase), confirmed after 3 months and after 6 months, did not demonstrate that there was a statistically significant difference between ozanimod 1 mg and interferon beta1a. The hazard ratios (HRs) for between-group differences for time to onset of disability progression confirmed after 3 months and 6 months were 0.95 (95% CI, 0.68 to 1.33; P = 0.765) and 1.41 (95% CI, 0.92 to 2.17; P = 0.112), respectively. Although patients in the ozanimod 1 mg groups exhibited fewer gadolinium (Gd)-enhanced brain lesions on magnetic resonance imaging (MRI) and fewer new or enlarged hyperintense T2 brain lesions on MRI per year relative to baseline than patients in the interferon beta1a groups in both trials, there was a substantial amount of missing data for these outcomes (24% and 14% of the data were missing in the RADIANCE Part B and SUNBEAM studies, respectively), which increases the uncertainty around the clinical benefits of ozanimod compared with interferon beta1a.
2. There is insufficient evidence to determine if ozanimod offers any meaningful clinical benefits compared with other disease-modifying treatments (DMTs) for RRMS. Direct comparative evidence for ozanimod 1 mg with DMTs other than interferon beta1a was not identified; however, interferon beta-1a is no longer a routinely used treatment option in current clinical practice, in part because of its modest efficacy, which limits the scope of the results obtained from RADIANCE Part B and SUNBEAM studies. Furthermore, limitations associated with the indirect comparison provided by the sponsor and reviewed by CADTH precluded any conclusions regarding the comparative efficacy and safety advantages of ozanimod with other disease-modifying options for RRMS due to the significant heterogeneity (varying study phase, blinding, diagnostic criteria, publication date, and mean duration of disease) across the included clinical trials.
3. Given the uncertainty in the clinical effectiveness of ozanimod relative to other DMTs, the cost-effectiveness of ozanimod is highly uncertain. CDEC noted that this was highlighted in the CADTH reanalyses, where, in some circumstances, there is no price at which ozanimod would be cost-effective at a $50,000 per QALY threshold.

Discussion Points

- RRMS is a seriously debilitating and chronic disease. CDEC discussed several unmet therapeutic needs that exist for patients with RRMS. Despite the currently available non-interferon DMTs used in the treatment of RRMS, including four other oral therapies, there remains an unmet need for a drug that effectively control MS symptoms and delay or halt disability progression with minimal adverse effects. However, CDEC could not confirm that ozanimod would adequately address the unmet need due in part to the uncertain meaningful benefit of ozanimod in delaying disability progression.
- RADIANCE Part B and SUNBEAM studies assessed health-related quality of life (HRQoL) using both mental and physical summary scores of the Multiple Sclerosis Quality of Life-54 (MSQOL-54). CDEC discussed that the potential benefit of ozanimod on HRQoL remains unknown mainly because the MSQOL-54 was not included in the statistical testing hierarchy.

Background

Ozanimod has a Health Canada indication for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations. Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator. Ozanimod is administered orally and is available as 0.23 mg, 0.46 mg, and 0.92 mg capsules of ozanimod hydrochloride. The Health Canada–recommended initial dose escalation regimen of ozanimod is 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7. The maintenance dosage is 0.92 mg once daily taken orally starting on day 8.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of randomized controlled trials of ozanimod, a network meta-analysis submitted by the sponsor, a match-adjusted indirect comparison (MAIC) that was identified in a literature search, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with RRMS and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group submission authored by the Multiple Sclerosis Society of Canada was received for this review, with patient perspectives obtained from an online survey. The following is a summary of key input from the perspective of the patient group:

- MS is characterized by symptoms that have a detrimental impact on patients' lives: fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. In addition, patients can also experience issues with balance, sexual dysfunction, spasticity, tremor, weakness, and difficulties with speaking and swallowing.
- Patients noted that depending on the type and severity of the symptoms, an individual's quality of life can be greatly impacted. Living with MS creates employment issues, such as the inability to maintain a stable job or remain in the workplace due to relapses, symptoms, medication side effects, and disability progression.
- Patients emphasized the importance of having therapies that effectively control their MS symptoms with minimal adverse effects and impacts on their quality of life. Despite the wide range of DMTs currently available, some patients are still struggling with inadequate therapeutic response and significant adverse effects.
- Patients placed high value in having a choice to select the administration, dosing schedule, side-effect profile, and level of medication monitoring that best fits their lifestyle and personal preference.

Clinical Trials

The systematic review conducted by CADTH included 2 studies (RADIANCE Part B and SUNBEAM). The RADIANCE Part B (N = 1,320) and SUNBEAM (N = 1,346) studies were multi-centre, randomized, double-blind, double-dummy, active-controlled, parallel-group phase III randomized controlled trials designed to evaluate the efficacy and safety of ozanimod in the treatment of adult patients with relapsing forms of MS. The main difference between the 2 phase III studies was the duration of treatment, which was 24 months for the RADIANCE Part B study and up to approximately 22 months (mean duration = 13.6 months) for the SUNBEAM study, in which treatment was continued until all patients received a minimum of 12 months of treatment. Patients were randomized 1:1:1 to receive either ozanimod 1 mg once daily orally, ozanimod 0.5 mg once daily orally, or interferon beta1a 30 mcg intramuscularly weekly in a double-dummy manner. The primary objective of both studies was to assess whether the clinical efficacy of ozanimod is superior to interferon beta1a in reducing the rate of confirmed clinical relapses based on the ARR in patients with relapsing MS.

A key limitation of both trials was the differential dropout rate (discontinuation from study) with more patients discontinuing in the interferon beta1a groups compared with the ozanimod 1 mg groups, where in the RADIANCE Part B study 10.4% of patients in the ozanimod 1 mg treatment group discontinued compared to 15.1% of patients in the interferon beta1a group, and in the SUNBEAM study 6.5% and 8.0% of patients discontinued the ozanimod 1 mg and interferon beta1a treatment groups, respectively. This difference between the treatment groups may be an indication that the rate of withdrawal may have been influenced by unblinding or post-randomization events. The apparent reduction in the lesion numbers in the ozanimod 1 mg treatment group relative to the interferon beta1a treatment group were not reflective of the whole intention-to-treat population because of the quantity of missing

data (24% in the RADIANCE Part B study and 14% in SUNBEAM study), which introduces a potential bias into the analysis. Both the RADIANCE Part B and SUNBEAM studies mainly included Eastern European centres, which were almost exclusively White, and included few North American centres. There was only 1 Canadian patient from 1 centre.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following: relapse-related outcomes, imaging outcomes, HRQoL, mobility, and disease progression. The primary outcome in the RADIANCE Part B study was confirmed ARR at the end of month 24; in SUNBEAM study, it was ARR during the treatment period.

- The occurrence of relapses were reported as an ARR based on the number of confirmed MS relapses. A relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS that persisted for at least 24 hours, were not attributable to confounding clinical factors, and were immediately preceded by a relatively stable or improving neurological state for 30 days or more. Clinical relapse was confirmed by the treating investigator when it was accompanied by objective neurologic worsening, as measured by a change in the Expanded Disability Status Scale (EDSS) score.
- MRI provides sensitive and quantitative measures of MS disease activity. Although there is no single MRI assessment that is accepted as predictive of clinical disease, key MRI end points included in MS studies assess aspects of the disease, such as active inflammation (Gd-enhanced T1 brain lesions) as well as accumulation of disease burden (e.g., hyperintense T2-weighted brain lesions) that are related to clinical disease activity and disability. Hyperintense T2-weighted brain lesions on MRI in MS reflect processes as diverse as edema, inflammation, demyelination, axonal loss, and gliosis, and are reflective of the overall burden of disease. An increase in hyperintense T2-weighted brain lesions on MRI is associated with more brain atrophy. In MS, Gd enhancement represents the leakage of Gd into the perivascular space as a result of local breakdown of the blood brain barrier due to inflammation. Changes in brain volume are a cumulative measure of disease activity. The number of new or enlarged T2-weighted lesions over 12 months and 24 months were key secondary end points in the SUNBEAM and RADIANCE Part B studies, respectively. The number of Gd-enhanced lesions at month 12 in the SUNBEAM study and at month 24 in the RADIANCE Part B study was a key secondary end point. Other secondary end points were the proportion of patients who were free of Gd-enhanced lesions at month 12 in the SUNBEAM study and at month 24 in the RADIANCE Part B study, the proportion of patients who were free of new or enlarged T2 lesions at month 12 in the SUNBEAM study and at month 24 in the RADIANCE Part B study, and percent change in normalized brain volume (atrophy) on brain MRI scans from baseline to month 12 in the SUNBEAM study and to month 24 in the RADIANCE Part B study.
- HRQoL was assessed using the MSQOL-54. The MSQOL-54 is a self-reported, disease-specific quality-of-life instrument. It contains 12 subscales, 2 summary scores, and 2 additional single-item measures. The subscales include physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function, while the additional single-item measures are satisfaction with sexual function and change in health. There is no single overall score for MSQOL-54, although the 2 summary scores — physical health and mental health — can be derived from a weighted combination of scale scores, which range from 0 to 100, with a higher score indicating improved quality of life. Change in MSQOL-54 scores from baseline to month 12 in the SUNBEAM study and to month 24 in the RADIANCE Part B study were other secondary end points.
- Mobility was assessed using the Multiple Sclerosis Functional Composite (MSFC). The 3 components of the MSFC assess different clinical dimensions: arm (9-Hole Peg Test [9-HPT]: the time needed to insert and remove 9 pegs), leg (Timed 25-Foot Walk [T25-FW]: the time needed to walk 25 feet), and cognition (Paced Auditory Serial Addition Test [PASAT]: the total number of correct additions). For the 9HPT and T25-FW tests, a higher test result means the patient worsened from baseline. For PASAT, a higher test result means that the patient improved from baseline.
- The time to onset of disability progression, as defined by a sustained worsening in EDSS score of 1.0 point or more, was confirmed after 3 months and 6 months.

Efficacy

In the RADIANCE Part B study, the adjusted ARRs in patients in the ozanimod 1 mg treatment group and interferon beta1a treatment group were 0.17 (95% CI, 0.14 to 0.21) and 0.28 (95% CI, 0.23 to 0.32), respectively. This corresponded to a relative percent reduction in ARR of 37.66% (95% CI, 23.22% to 49.39%; $P < 0.0001$) in favour of ozanimod 1.0 mg. Similarly, in the SUNBEAM study, the adjusted ARRs in patients in the ozanimod 1 mg treatment group and interferon beta1a treatment group were 0.18 (95% CI, 0.14 to 0.24) and 0.35 (95% CI, 0.28 to 0.44), respectively. This corresponded to a relative percent reduction in ARR of 48.21%

(95% CI, 33.70% to 59.55%; P < 0.0001) in favour of ozanimod 1.0 mg. This reduction was also considered to be clinically relevant by the clinical expert consulted by CADTH.

The number of new or enlarged hyperintense T2-weighted brain lesions on MRI and the number of Gd-enhanced brain lesions on MRI were included in the pivotal trials as key secondary outcomes, which were also included in the statistical testing hierarchy. Ozanimod 1 mg demonstrated superiority to interferon beta1a in terms of the number of new or enlarged hyperintense T2-weighted brain lesions on MRI with a percent reduction in new or enlarging hyperintense T2 lesions in favour of ozanimod 1.0 mg of 42.35% (95% CI, 28.58% to 53.47%; P < 0.0001) and 48.33% (95% CI, 37.47% to 57.30%; P < 0.0001) in the RADIANCE Part B and SUNBEAM studies, respectively. Similarly, ozanimod 1 mg was superior to interferon beta1a in terms of the number of Gd-enhanced brain lesions on MRI with a 52.94% (95% CI, 27.53% to 69.45%; P = 0.0006) and 62.97% (95% CI, 46.41% to 74.42%; P < 0.0001) percent reduction in the number of Gd-enhanced brain lesions on MRI in the RADIANCE Part B and SUNBEAM studies, respectively. Although ozanimod 1 mg achieved statistical significance in the reduction in the number of lesions over the interferon beta1a group, the quantity of missing data (24% in the RADIANCE Part B study and 14% in the SUNBEAM study) makes the accuracy of the estimates of the lesion numbers and the P values uncertain, which introduces a potential bias into the analysis.

In the RADIANCE Part B study, the between-group difference for the physical health composite summary score was 1.35 (95% CI, −0.25 to 2.94; P = 0.098) and for the mental health composite summary score it was 0.38 (95% CI, −1.55 to 2.31; P = 0.699). In the SUNBEAM study, ozanimod was favoured when compared with the interferon beta1a group for the physical health composite summary score of the MSQOL-54 at month 12; the difference between the treatment groups was 1.64 (95% CI, 0.10 to 3.18; nominal P = 0.036), which exceeded the estimated minimal important difference of 1.5. However, the MSQOL-54 was not included in the statistical testing hierarchy. The between-group difference for the mental health composite summary score in the SUNBEAM study was 0.36 (95% CI, −1.52 to 2.23; P = 0.710).

There were no differences between treatment groups for the assessment of MSFC, T25-FW, and 9-HPT in both the SUNBEAM and RADIANCE Part B studies.

The pooled analyses of the RADIANCE Part B and SUNBEAM studies for time to onset of disability progression did not demonstrate a statistically significant difference between ozanimod 1 mg and interferon beta1a; the HRs for between-group differences for time to onset of disability progression confirmed after 3 months and 6 months were 0.95 (95% CI, 0.68 to 1.33; P = 0.765) and 1.41 (95% CI, 0.92 to 2.17; P = 0.112), respectively.

Harms (Safety)

In the RADIANCE Part B study, the majority of patients reported at least 1 treatment-emergent adverse event, in which 324 patients (74.7%) in the ozanimod 1 mg group and 365 patients (83.0%) in the interferon beta1a group experienced at least 1 treatment-emergent adverse event. In SUNBEAM study, 268 patients (59.8%) in the ozanimod 1 mg group and 336 patients (75.5%) in the interferon beta1a group experienced at least 1 treatment-emergent adverse event. In both studies, influenza-like illness, upper respiratory tract infection, and pyrexia were reported in a greater proportion of patients in the interferon beta1a group (influenza-like illness: 48.9% to 51.0%; upper respiratory tract infection: 4.4% to 8.4%; pyrexia: 6.3% to 6.4%) than in the ozanimod 1 mg group (influenza-like illness: 3.8% to 6.2%; upper respiratory tract infection: 4.0% to 7.8%; pyrexia: 1.1% to 2.5%). The overall higher incidence of adverse events (AEs) in the interferon beta1a treatment group compared with the ozanimod treatment groups could be attributed to the predominance of influenza-like illness and pyrexia events.

In the RADIANCE Part B study, serious adverse events (SAEs) were reported by 28 patients (6.5%) in the ozanimod 1 mg group and by 28 patients (6.4%) in the interferon beta1a group. In SUNBEAM study, SAEs were reported by 13 patients (2.9%) in the ozanimod 1 mg group and by 11 patients (2.5%) in the interferon beta1a group. In the RADIANCE Part B study, SAEs that occurred in more than 1 patient in any treatment group were appendicitis (ozanimod 1 mg: n = 2; 0.5%; interferon beta1a: n = 2; 0.5%), and ovarian cyst (ozanimod 1 mg: n = 2; 0.5%; interferon beta1a: n = 0). In the SUNBEAM study, no SAE was reported in more than 1 patient in either treatment group.

The proportion of patients who stopped treatment due to AEs was also low, ranging from 2.9% and 4.1% of patients across the 2 pivotal trials, and was similar between treatment groups in each study.

No deaths were reported during the SUNBEAM study. In the RADIANCE Part B study, 1 death due to chronic kidney failure occurred in the ozanimod 1 mg group.

AEs of special interest were rare. The only events that occurred in more than 1 patient in the RADIANCE Part B study were increased alanine aminotransferase (ALT) in 6 (1.4%) patients in the ozanimod 1 mg group and 8 (1.8%) patients in the interferon beta1a group, increased aspartate aminotransferase (AST) in 5 (1.1%) patients in the interferon beta1a group, increased transaminases in 2 (0.5%) patients in the ozanimod 1 mg group, increased blood pressure in 3 (0.7%) patients in the ozanimod 1 mg group, and macular edema in 2 (0.5%) patients in the interferon beta1a group. In the SUNBEAM study, the events that occurred in more than 1 patient were increased ALT and increased blood pressure, which were reported in 3 (0.7%) and 4 (0.9) patients, respectively, in the ozanimod 1 mg group.

Indirect Treatment Comparisons (If Applicable)

Two indirect treatment comparisons (ITCs) were identified, reviewed, and critically appraised: 1 submitted and commissioned by the sponsor and 1 that was published. The sponsor-submitted ITC conducted a systematic review and used Bayesian network meta-analysis to evaluate the relative clinical efficacy and safety of ozanimod 1 mg compared with other RRMS treatments in adult patients with RRMS. The published ITC used an MAIC to compare ozanimod to fingolimod in patients with RRMS using individual patient data from the RADIANCE-B and SUNBEAM trials to match and adjust patients to those included in the comparator trials.

The sponsor-submitted ITC reported that ozanimod was favoured in reducing ARR compared to interferons, glatiramer acetate, and teriflunomide, and was less efficacious than ocrelizumab, alemtuzumab, and natalizumab. For confirmed disability progression at 12 weeks, there was no difference between ozanimod and all treatments included in the network except for alemtuzumab and ocrelizumab, which were favoured compared to ozanimod. For confirmed disability progression at 24 weeks, Betaseron, cladribine, alemtuzumab, natalizumab, and ocrelizumab were favoured when compared with ozanimod. For SAEs, ozanimod was not better or worse than any other treatment. However, the analysis found ozanimod to be associated with similar or lower odds of AEs compared with interferon beta1a, glatiramer acetate, peginterferon beta1a, dimethyl fumarate, and alemtuzumab. However, the degree to which the various sources of heterogeneity were accounted for prevented drawing definitive conclusions regarding the comparative efficacy and safety of ozanimod, where clinical heterogeneity was present in the analysis due to varying study phases, blinding, diagnostic criteria, publication date, and mean duration of disease. In addition, the definitions for “relapse” and “disease progression” were not provided; hence it was not possible to know whether the definition for these two outcomes was consistent across studies.

The published MAIC reported that ozanimod and fingolimod were comparable in reducing ARRs and the proportion of patients with confirmed disability progression. Ozanimod was also reported to be associated with lower risk of AEs over 1 year and 2 years of follow-up compared with fingolimod. However, there was substantial uncertainty in the MAIC results. Hence, a firm conclusion cannot be drawn from these results.

Cost and Cost-Effectiveness

Ozanimod is an oral capsule available in 3 strengths: 0.23 mg, 0.46 mg, and 0.92 mg. The recommended dosage is 0.23 mg for days 1 to 4, 0.46 mg for days 5 to 7, and 0.92 mg daily thereafter. At a unit cost of $68.49 per capsule regardless of strength, the annual cost of treatment with ozanimod is $25,017 per patient.

The sponsor submitted a cost-utility analysis based on a cohort multi-state Markov model to simulate the disease course of RRMS patients receiving treatment with ozanimod versus other DMTs, including ocrelizumab, interferon beta1a (Avonex, Rebif), interferon beta-1b (Betaseron, Extavia), peginterferon beta1a (Plegridy), glatiramer acetate (Copaxone, Glatect), teriflunomide, dimethyl fumarate, natalizumab, cladribine, fingolimod (Gilenya and generic), and alemtuzumab. The model was based on patients transitioning across EDSS states 0 to 9, transitioning from RRMS to secondary progressive multiple sclerosis (SPMS), and death. Thus, the model consisted of 21 states (10 RRMS, 10 SPMS, and death). Patients with RRMS entered the model in an EDSS state between 0 and 5. In each cycle, patients could transition between EDSS states and between RRMS and SPMS or enter the absorbing death state. Treatment efficacy was based on ARRs and disease progression, which was taken from a sponsor-submitted ITC. The analysis was conducted from the perspective of the public health care payer, over a 25-year time horizon with 1-year cycle lengths, with half-cycle correction applied to estimates of life-years and quality-adjusted life-years (QALYs).

CADTH identified the following key limitations with the sponsor’s pharmacoeconomic analysis:

- The sponsor adopted a more favourable assumption regarding the treatment effectiveness for ozanimod for disease progression than estimated from their ITC. CADTH used the ITC estimate in reanalyses.
- The sponsor adopted a 25-year time horizon. This was argued to address uncertainty about duration of treatment effect. However, applying a treatment waning effect is a more appropriate way to account for the impact of treatment duration.

- The sponsor's analysis did not include best supportive care (BSC) as a comparator. Based on recommendations within the CADTH Guidelines, BSC should be considered when new technologies have not been fully adopted by the decision-maker(s), or newer technologies represent uncertain (or poor) value. This also aligns with previous CADTH reviews for MS therapies.

In the CADTH base case, a treatment waning effect was applied, effect estimates from the ITC were used, and BSC was included as a comparator. CADTH found that ozanimod was associated with lower health benefits (fewer QALYs) than all currently available active therapies. Even with substantial price reductions, ozanimod would not be considered a cost-effective therapy as any cost savings could not compensate for the reduction in QALYs at a $50,000 per QALY threshold. When reimbursement is restricted to first-line use only, ozanimod may represent a cost-effective option at a $50,000 per QALY threshold despite producing fewer health benefits (QALYs) than other DMTs if the price of ozanimod is substantially reduced (by 77%).

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 20, 2021, Meeting

Regrets

None

Conflicts of Interest

None

June 16, 2021 Meeting (Reconsideration)

Regrets

Three CDEC members did not attend.

Conflicts of Interest

None