CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

CLADRIBINE (MAVENCLAD — EMD SERONO)
Indication: Relapsing-Remitting Multiple Sclerosis

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee recommends that cladribine be reimbursed as monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability, if the following conditions are met:

Conditions:
- For use in patients who have had an inadequate response to, or are unable to tolerate, one previous therapy for RRMS, and who have had at least one relapse within the previous 12 months.
- The patient is under the care of a specialist who has experience in the diagnosis and management of RRMS.
- There is a price reduction.

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- The patient is under the care of a specialist who has experience in the diagnosis and management of RRMS.
- There is a price reduction.

Reasons for the Recommendation:

1. In one double-blind, randomized controlled trial (RCT) of patients with RRMS who had at least one relapse within 12 months before study entry and who had not had two or more previous disease-modifying therapies (CLARITY, N = 1,326), cladribine was superior to placebo for reducing annualized relapse rates (rate ratio of 0.43; 95% confidence interval [CI], 0.34 to 0.54, $P < 0.001$). Furthermore, cladribine was associated with a decreased risk of confirmed disease progression sustained for three months as compared with placebo (hazard ratio of 0.67; 95% CI, 0.48 to 0.93, $P = 0.018$).
2. Cladribine provides an alternative disease-modifying therapy for patients with RRMS. It also offers a different safety profile relative to other disease-modifying therapies for RRMS.
3. The manufacturer–submitted price of cladribine is $3,082.70 per 10 mg tablet. The CADTH Common Drug Review (CDR) re-analysis of the manufacturer-provided cost-utility analysis indicated that cladribine is unlikely to be a cost-effective treatment for patients with RRMS either in the total population or in the specific subpopulations considered.
4. There is insufficient evidence to determine if cladribine offers any meaningful clinical benefits compared with other disease-modifying therapies for RRMS. CLARITY compared cladribine with placebo and not an active comparator. Furthermore, limitations associated with the indirect comparison provided by the manufacturer and reviewed by CDR precluded any definitive conclusions regarding the comparative efficacy and safety advantages of cladribine with other disease-modifying options for RRMS.

Implementation Considerations:

Based on the CDR re-analyses, a price reduction would be needed to achieve a cost per quality-adjusted life-year (QALY) of $50,000, as compared with fingolimod. CDEC noted that the percentage reduction may need to be greater based on the pricing of alternative disease-modifying therapies for RRMS.

Discussion Points:

- The Health Canada indication for cladribine states that it is generally recommended for RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS; however, most patients enrolled in CLARITY were treatment-naive. Health Canada expressed concern about the higher proportions of patients treated with cladribine in CLARITY who experienced certain notable adverse events, such as lymphopenia, herpes zoster infection, and neoplasms, as compared with placebo. As a result, Health Canada's benefit-risk evaluation for cladribine was that it should generally not be used as a first-line drug in the treatment of RRMS.
- RRMS is a seriously debilitating disease that is chronic in nature. CDEC discussed the unmet therapeutic need for patients with RRMS and that although there are currently seven other available non-interferon, disease-modifying drugs indicated for the treatment of RRMS, including three other oral therapies, there remains a need for drugs with alternative modes of administration

and action. Moreover, many of the disease-modifying drugs used as second-line (or later-line) are associated with potentially serious adverse effects; cladribine may offer an alternative treatment with a different safety profile.

- A disease-specific as well as a generic health-related quality of life assessment tool were used in CLARITY to explore the study drug's quality of life benefits. Statistical significance in favour of cladribine as compared with placebo was achieved for between-group differences on the generic health-related quality of life assessment tool only. The validity of the disease-specific health-related quality of life assessments were limited by the relatively small proportion of patients with evaluable data for this outcome. Therefore, the effects of cladribine on patients' health-related quality of life are uncertain.

Background:

Cladribine has a Health Canada indication as monotherapy for the treatment of adult patients with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability. Cladribine is generally recommended for RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS. Cladribine is an immunosuppressant. It is available as an orally administered tablet, and the Health Canada-approved dose is 3.5 mg/kg administered over a total course of treatment of two years.

Summary of CADTH's Canadian Drug Expert Committee Considerations:

CDEC considered the following information prepared by the CADTH CDR: a systematic review of one RCT of cladribine, an indirect comparison, and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from clinical experts with experience treating patients with RRMS, and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by RRMS.

Patient Input Information

One patient group responded to the call for patient input for this CDR review: the Multiple Sclerosis Society of Canada. The following is a summary of key input from the perspective of the patient group:

- Patient input submitted to CDR suggests that only half of the surveyed patients believed their current therapy to be effective in managing their disease. Patients noted several side effects characteristic of the various drugs used to treat MS, including injection site reactions, flushing, alopecia, skin rash/hives, joint/musculoskeletal pain, gastrointestinal and flu-like symptoms.
- Of the therapies currently available for MS, there is a mix of routes of administration (i.e., oral, injectable, and intravenous infusion), and patients identified this as being an important consideration with their therapy.
- None of the surveyed patients had experience with cladribine. Patients emphasized the importance of having more choices for the management of their disease, and this is particularly important for patients experiencing an inadequate response to their current therapy.

Clinical Trials

The systematic review included one double-blind RCT that compared two different dose regimens of cladribine with placebo in a population of patients with RRMS.

CLARITY randomized 1,326 patients 1:1:1 to cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, or placebo over a two-year treatment course. Only the Health Canada–recommended cladribine dose of 3.5 mg/kg was of interest. Eight per cent of patients treated with cladribine 3.5 mg and 13% of placebo-treated patients withdrew from the study.

No active comparator trials met the inclusion criteria for this systematic review. Other limitations included the fact that key efficacy outcomes such as health-related quality of life and disability progression were not adjusted for multiple statistical comparisons, and a considerable amount of data were missing for all health-related quality of life outcomes.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: relapses, disability progression, and MRI findings. Health-related quality of life was discussed but limited conclusions could be drawn due to the large amount of missing data. Health-related quality of life is a key issue noted by patients in their input to CDR. The primary outcome in the CLARITY trial was the annualized relapse rate.

- *Annualized relapse rate,* was calculated as the total number of relapses divided by the total number of days on study multiplied by 365.25. A relapse was defined as a two grade increase in one or more Kurtzke Functional Systems (KFS) or one grade in two or more KFS, not including changes in bowel/bladder function or cognition, in the absence of fever, and lasting for at least 24 hours, all preceded by at least 30 days of clinical stability or improvement. Relapses were to be documented and followed up through neurological assessments. Patients were told to inform the trial site within 24 hours of a suspected relapse, at which time the trial personnel (with the exception of the evaluating physician) reviewed the symptoms with the patient and determined whether a neurological assessment was indicated.
- *Disability progression,* defined as time to a sustained change in Expanded Disability Status Scale (EDSS) of ≥ 1 point, or ≥ 1.5 points if the baseline EDSS score was 0, over a period of at least three months, was a secondary outcome of CLARITY. It was not adjusted for multiplicity. The EDSS evaluation was carried out by a blinded evaluating physician, who was not aware of data from the patient's prior evaluations. The EDSS is a 10-point ordinal scale used to assess disability in MS. It assesses eight different domains of disability: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. The minimal important clinical difference (MCID) from 0 to 5.5 is 1.0, and the MCID from 5.5 to 8.5 is 0.5.
- *MRI outcomes* were assessed as part of the statistical hierarchy and thus were controlled for multiplicity: T1 gadolinium-enhancing lesions, active T2 lesions, as well as combined unique lesions, which were defined as 1) new T1 gadolinium-enhancing or 2) new T2 non-enhancing or enlarging lesions, or 3) both, without double-counting. Other MRI parameters assessed included brain atrophy, measured by per cent change in brain volume, as a post hoc analysis.
- *Health-related quality of life* was assessed using three scales. The Multiple Sclerosis Quality of Life-54 (MSQoL-54) items is a self-reported, disease-specific quality of life instrument, based on the SF-36 instrument, supplemented with 18 disease-specific dimensions measuring anxiety provoked by the patient's health status (four items); sexual functioning (four items); satisfaction with sex life (one item); overall quality of life (two items); cognitive functioning (four items); energy (one item); pain (one item); and social functioning (one item). The MSQoL-54 was available in three languages, limiting the number of patients that could be involved in the assessment. The EuroQoL-5-Dimensions (EQ-5D) questionnaire is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (≥ 12 years old) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights. The second part is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-5D VAS that best represents their health on that day. Short-Form (36) Health Survey (SF-36) was also assessed; however, since no baseline data were collected, CDR did not report this outcome.
- *Freedom from disease activity* was assessed as a post hoc analysis, and was composed of three outcomes assessed in the pre-planned analysis for CLARITY: patients with no relapses during the study, no three-month sustained change (worsening) in EDSS score, and no new MRI lesions (no T1 gadolinium-enhancing or active T2 lesions).

Efficacy

- Cladribine was superior to placebo for the primary outcome, with a reduced annualized rate of relapses in the cladribine versus placebo group (rate ratio of 0.43; 95% confidence interval [CI], 0.34 to 0.54; $P < 0.001$). The annualized relapse rate for cladribine was 0.14 (95% CI, 0.12 to 0.17) and for placebo 0.33 (95% CI, 0.29 to 0.38), and 80% of cladribine-treated patients and 61% of placebo-treated patients were relapse-free over the course of the study.
- There was a lower risk of three-month sustained progression in disability at week 96, measured by the EDSS, with cladribine than with placebo (hazard ratio of 0.67; 95% CI, 0.48 to 0.93; $P = 0.018$). In the cladribine group, 86% of patients did not experience disability progression versus 79% in the placebo group. These outcomes were not controlled for multiple statistical comparisons and thus should be interpreted cautiously.

- Health-related quality of life was assessed using the MSQoL-54, the EQ-5D, and the SF-36. The MSQOL-54 and SF-36 were added in late protocol amendments, and as a result only approximately 10% of the population had baseline and end-of-study data for MSQoL-54, and there were no baseline data for the SF-36. EQ-5D VAS and index scores were missing for approximately 20% of the randomized population, and there was a statistically significant improvement in EQ-5D VAS and index scores for cladribine versus placebo. However, neither of these *P* values were adjusted for multiple statistical comparisons and therefore these results should be interpreted cautiously.
- MRI outcomes such as T1- and T2-weighted MRI were key secondary outcomes of CLARITY and thus were controlled for multiple statistical comparisons. The number of T1 gadolinium-enhanced lesions per patient per scan at 96 weeks was reduced with cladribine versus placebo (treatment difference of −0.78; 95% CI, −0.92 to −0.65; $P < 0.001$), as was the number of active T2 lesions per patient per scan at 96 weeks (treatment difference of −1.05; 95% confidence interval of −1.22 to −0.87; $P < 0.001$).
- The proportion of patients who were considered free of disease activity was higher with cladribine (47%) than with placebo (17%), and this difference was reported as statistically significant (odds ratio of 4.25; 95% CI, 3.03 to 5.96; $P < 0.0001$). However, this was a post hoc analysis, and data were missing for 10% of the cladribine group and 17% of the placebo group.

Harms (Safety)

- In CLARITY, similar proportions of patients experienced serious adverse events with cladribine (8% of patients) and placebo (6% of patients). Pneumonia (1% of patients in each group), uterine leiomyoma (1% in cladribine, none in placebo) and lymphopenia (1% in cladribine, none in placebo) were the most common serious adverse events. There were two deaths in each of the cladribine (acute myocardial infarction, pancreatic cancer) and placebo (suicide, cerebrovascular accident) groups.
- Overall adverse events occurred in 81% of cladribine-treated versus 73% of placebo-treated patients. Headache, occurring in 24% of cladribine-treated and 17% of placebo-treated patients, and lymphopenia (22% of cladribine versus 2% of placebo) were the most commonly reported adverse events. This numerical difference in the proportion of patients with lymphopenia is consistent with the mechanism of action of cladribine.
- The proportion of patients who withdrew due to an adverse event was similar in cladribine and placebo groups (1% of patients in each). There were no clear trends among specific reasons for withdrawing due to an adverse event.
- Notable harms included infections, hematological issues, and malignancies. Herpes zoster infection occurred in 2% of cladribine-treated (eight patients) versus no placebo patients. There were no notable differences in risk of other infections between groups. As noted, lymphopenia was more common with cladribine than placebo. Benign, malignant, or unspecified neoplasms (including cysts and polyps) occurred in 4% of cladribine-treated versus 2% of placebo patients. The potential association between cladribine and malignancies has not been fully elucidated. No cases of progressive multifocal leukoencephalopathy with oral cladribine have been reported in patients with RRMS.
- Cladribine is somewhat unique in that it is dosed in a two-year cycle. CLARITY was a 96-week study, corresponding to the two-year course of cladribine, and thus the comparative safety of cladribine beyond this initial double-blind comparative phase is uncertain. CLARITY EXT was an extension to the CLARITY trial, in which patients were either continued on cladribine or switched to cladribine from placebo. However, there were methodological limitations with this extension study that limit conclusions that can be drawn about the longer-term safety of cladribine.

Network Meta-Analyses

One manufacturer-provided indirect comparison based on network meta-analyses was reviewed and critically appraised by CDR. The network meta-analyses suggested that cladribine was associated with lower annualized relapse rates in the overall population analyzed than several other disease-modifying therapies, including interferon beta-1a and beta-1b, teriflunomide, glatiramer acetate, and peginterferon beta-1a. Cladribine was reported as being superior to placebo only with respect to reducing confirmed disease progression sustained for three and six months at 24 months. However, the limited transparency in the reporting of methods and results, as well as the degree to which the various sources of heterogeneity were accounted for, prevented drawing definitive conclusions regarding the comparative efficacy of cladribine. Subgroup analyses in high disease activity (HDA) and treatment-experienced populations were difficult to interpret given the sparse networks and issues with defining the populations from the included studies. The analysis of safety end points in the indirect comparisons was limited to aggregate outcomes (i.e., total adverse events), but 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

Cladribine is available as a 10 mg tablet at a price of $3,082.70 per tablet. The recommended cumulative dose is 3.5 mg/kg over the course of two years, with one treatment course of 1.75 mg/kg per year. The average annual cost is $43,158 based on a patient weight of 70 kg.

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing cladribine with other available disease-modifying drugs. The analysis was conducted for two distinct patient populations: the pre-treated group of adult patients with RRMS in Canada who had prior treatment with any disease-modifying drugs; and the HDA group with adult patients with RRMS in Canada who had at least one relapse in the previous year while on disease-modifying drug therapy and at least one T1 gadolinium-enhancing lesion or nine T3 lesions, or who had two or more relapses in the previous year whether or not on treatment. Comparators were limited to those disease-modifying drugs included in a network meta-analysis provided by the manufacturer. For the pre-treated population this was limited to fingolimod, while for the HDA population this was limited to fingolimod, natalizumab, and alemtuzumab. In the model, patients transitioned between EDSS states 0 through 9. For alemtuzumab and cladribine it was assumed that patients would take a maximum of two years of therapy, although re-initiation was allowed. Treatment was assumed to stop once patients reached EDSS 7. The analysis was run over a 25-year time horizon using an annual cycle length. The analysis adopted a Canadian public health care system perspective. The manufacturer reported that for pre-treated patients, cladribine dominated fingolimod (i.e., cladribine was associated with lower total costs and greater QALYs); and, for patients with HDA, cladribine dominated alemtuzumab, fingolimod, and natalizumab.

CDR identified a number of key limitations with the manufacturer's economic model that had a direct effect on the results of the analysis.

- The manufacturer's model allows for an improvement in EDSS state within a cycle; for some states the probability of improvement exceeded 10%. While there is some debate regarding this aspect of natural history in RRMS, the clinical expert suggested the assumption relating to patients improving was not justified. Hence, CDR adopted the transition matrix based on the London, Ontario, study, which did not allow improvement in EDSS.
- The manufacturer's base results were contingent on accepting the results of unpublished network meta-analyses specific to the pre-treated and HDA populations. There were a number of limitations identified by CDR clinical reviewers specifically relating to the use of post hoc subgroup analysis and the limited amount of similar data for other comparators. CDR adopted the approach of assuming equal efficacy with respect to annualized relapse rate and confirmed disability progression for these subgroups.
- Further, the manufacturer assumed a waning of treatment effect with all therapies except cladribine after one year, with effect sizes reduced by 75%. In the absence of comparative clinical data to support this assumption, CDR adopted the same treatment waning assumptions for all therapies.
- Finally, the manufacturer assumed that cladribine and alemtuzumab will be used for no longer than two years, and beyond two years patients were assumed to still be subject to the transition probabilities adjusted by the effectiveness of the therapy. CDR adopted an approach whereby all patients would stop treatment at two years and would then experience the transition probabilities associated with best supportive care.

CDR re-analysis incorporated all of the above concerns, used the London database for the best supportive care transition matrix, assumed equal treatment waning and withdrawal for all treatments, and assumed equal effectiveness for disease-modifying drugs in the specific subpopulations. In addition, CDR conducted and reported analysis for the full RRMS population given the concerns with the subgroup analyses.

For all RRMS patients, cladribine was subject to extended dominance by fingolimod and alemtuzumab; regardless of a decision-maker's willingness to pay for a QALY, cladribine would not be cost-effective. If a decision-maker is willing to pay $50,000 per QALY, the price of cladribine would need to be reduced by 15% when compared with fingolimod. For pre-treated patients, cladribine was dominated (associated with greater total costs and fewer QALYs) by fingolimod. For HDA patients, cladribine was dominated by fingolimod. Price reductions of 33% would be required if a decision-maker is willing to pay $50,000 per QALY when compared with fingolimod for pre-treated patients and HDA patients.

CDR was unable to consider any negotiated prices for available disease-modifying drugs.

May 15, 2018 Meeting:

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None

October 17, 2018 Meeting:

CDEC Members:

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None