CDEC FINAL RECOMMENDATION

ALEMTUZUMAB
(Lemtrada — Genzyme Canada)
Indication: Relapsing-Remitting Multiple Sclerosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that alemtuzumab be listed for the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies, if the following clinical criteria and conditions are met:

Clinical Criteria:
- At least two attacks (first episode or relapse) in the previous two years, with at least one attack in the previous year
- At least one relapse while on at least six months of interferon beta or glatiramer acetate within the last 10 years
- A Kurtzke Expanded Disability Status Scale (EDSS) score of 5 or less

Conditions:
- Reduction in price
- Funding limited to two years of therapy (i.e., eight doses; two treatment courses)
- Prescribed by a specialist with experience in the treatment of multiple sclerosis (MS)

Reasons for the Recommendation:
1. A multi-centre, active-controlled, parallel-group, randomized controlled trial (RCT) conducted in MS patients previously treated with disease-modifying therapies (CARE-MS II; N = 840) demonstrated that treatment with alemtuzumab was associated with a statistically significant reduction in annualized relapse rate (ARR) and in the risk of sustained accumulation of disability (SAD) over two years of treatment compared with patients treated with interferon beta-1a (Rebif).
2. The CADTH Common Drug Review (CDR) base-case analysis suggested that alemtuzumab is associated with an incremental cost-utility ratio (ICUR) of approximately $31,000 compared with Rebif in adult patients with active RRMS who had previously failed or were intolerant to interferon beta-1a or glatiramer acetate. However, CDR reanalyses demonstrated that there was substantial variability within the pharmacoeconomic evaluation, ranging from alemtuzumab dominating Rebif to $91,000 per quality-adjusted life-year

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(QALY) for alemtuzumab compared with Rebif. CDEC concluded that a reduction in price would increase the probability that alemtuzumab is a cost-effective alternative to Rebif.

3. To be eligible for CARE-MS II, patients were required to have an EDSS score of 0 to 5 at the time of screening.

Background:

Alemtuzumab is a recombinant anti-CD52 antibody that is thought to exert its effect through the depletion of autoreactive T and B lymphocytes and subsequent rebalancing of the immune system. Alemtuzumab is indicated for use as monotherapy for the management of patients with RRMS who have had an inadequate response to interferon beta or other disease-modifying therapies. Alemtuzumab is available as a concentrated solution for infusion as 1.2 mL (10 mg/mL) single-use vials.

The recommended dose of alemtuzumab is 12 mg/day administered by intravenous (IV) infusion over a period of approximately four hours for two treatment courses:

- Initial course: 12 mg/day for five consecutive days (60 mg total dose)
- Second course: 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of alemtuzumab RCTs, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with MS.

Patient Input Information

The following is a summary of key information provided by two patient groups that responded to the CDR call for patient input:

- MS is characterized by symptoms that have a detrimental impact on patients' lives: fatigue, pain, difficulty walking, memory or attention problems, bladder problems, numbness or tingling, heat intolerance, and electric shock sensations.
- People living with RRMS indicated that the disease had a significant impact on their physical activity, quality of life, mental health, work, and their family members and caregivers.
- Current MS therapies reduce the frequency and severity of relapse and may slow disability progression; however, they are limited by their high cost, side effects, the need for frequent injections or infusions, and waning effectiveness over time for many.

Clinical Trials

One two-year, randomized, active-controlled study was included in the CDR systematic review. CARE-MS II (N = 840) included patients with active RRMS (according to the McDonald 2005 criteria) who had previously experienced a relapse while on at least six months of interferon beta or glatiramer acetate. Patients were randomized to receive alemtuzumab (24 mg or 12 mg) over two treatment cycles (five consecutive days at month 0 and three consecutive days at month 12) or interferon beta-1a 44 mcg three times per week. Randomization to alemtuzumab 24 mg was closed after a protocol amendment and results were not considered in the CDR

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review. All patients received methylprednisolone at month 0 and month 12 (1 g/day for three consecutive days) for prophylaxis against infusion-associated reactions. Following a protocol amendment, patients randomized to alemtuzumab also received acyclovir (200 mg twice daily starting the first day of each treatment cycle and continuing for 28 days after that last day) for prophylaxis against herpes simplex virus reactivation.

Outcomes

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

- Relapse — defined as any new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability with an objective change on neurological examination.
- SAD — defined as an increase in EDSS from baseline of ≥ 1 point, or ≥ 1.5 points if the baseline EDSS was 0, confirmed over three or six months. EDSS is an ordinal scale (0 to 10) that assesses eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation.
- Multiple Sclerosis Functional Composite (MSFC) — used to assess ambulation, upper limb dexterity, and cognition using the following: timed 25-foot walk, nine-hole peg test, and paced auditory serial addition test.
- Health-related quality of life — assessed using the Functional Assessment of Multiple Sclerosis (FAMS), the Short Form (36) Health Survey (SF-36), and the EuroQol 5-Dimensions Questionnaire (EQ-5D).
- Magnetic resonance imaging (MRI) — used to assess changes in the number and volume of lesions.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

In CARE-MS II, the co-primary end points were ARR and time to six-month SAD.

Efficacy

- The adjusted ARR was statistically significantly lower in the alemtuzumab group compared with the interferon beta-1a group; rate ratio 0.51 (95% confidence interval [CI], 0.39 to 0.65).
- The proportion of patients with six-month SAD over two years was statistically significantly lower for the alemtuzumab group compared with the interferon beta-1a group (hazard ratio 0.58 [95% CI, 0.38 to 0.87]).
- The change from baseline in EDSS score at two years was –0.17 (95% CI, –0.29 to –0.05) in the alemtuzumab group and 0.24 (95% CI, 0.07 to 0.41) in the interferon beta-1a group; mean difference –0.41 (95% CI, –0.61 to –0.22).
- There was no statistically significant difference between alemtuzumab and interferon beta-1a in the percentage change from baseline in T2-hyperintense lesion volume.
- The change from baseline in MSFC scores was 0.08 (95% CI, 0.04 to 0.12) in the alemtuzumab group and –0.04 (95% CI, –0.10 to 0.02) in the interferon beta-1a group.
- The change from baseline in the overall FAMS score was 6.20 (95% CI, 3.69 to 8.71) in the alemtuzumab group and 0.85 (95% CI, –2.69 to 4.40) in the interferon beta-1a group.
- The change from baseline in the mental component summary score of the SF-36 was 2.07 (95% CI, 1.03 to 3.11) in the alemtuzumab group and 1.33 (95% CI, –0.13 to 2.80) in the interferon beta-1a group. The change from baseline in the physical component summary

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score of the SF-36 was 2.51 (95% CI, 1.66 to 3.36) in the alemtuzumab group and 0.61 (95% CI, –0.58 to 1.80) in the interferon beta-1a group.
- The change from baseline in the EQ-5D utility score was 0.031 (95% CI, 0.006 to 0.055) in the alemtuzumab group and 0.018 (95% CI, –0.016 to 0.053) in the interferon beta-1a group. The change from baseline in the EQ-5D visual analogue scale score was 4.292 (95% CI, 2.507 to 6.076) in the alemtuzumab group and –0.98 (95% CI, –3.51 to 1.55) in the interferon beta-1a group.

Harms (Safety and Tolerability)
- Common adverse events with alemtuzumab include headache (52.9%), rash (44.4%), nasopharyngitis (29.4%), nausea (24.1%), and pyrexia (21.8%). The majority of patients in the alemtuzumab 12 mg group experienced an infusion-associated reaction (90.3%).
- A total of 19.5% of patients in the alemtuzumab group experienced a serious adverse event compared with 21.8% in the interferon beta-1a group.
- A total of 3.2% of patients in the alemtuzumab group and 8.9% of patients in the interferon beta-1a group discontinued study treatment due to an adverse event. The most common adverse events that led to discontinuation of treatment in the alemtuzumab group were infusion-associated reactions.
- Four patients were reported to have immune thrombocytopenic purpura (ITP) in the alemtuzumab group. A greater proportion of patients experienced a thyroid adverse event in the alemtuzumab group compared with the interferon beta-1a group (15.9% versus 5.0%). A greater proportion of patients experienced an infection with alemtuzumab 12 mg than with interferon beta-1a (76.8% versus 66.3%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing alemtuzumab with interferon beta-1a (Avonex and Rebif), glatiramer acetate, dimethyl fumarate, fingolimod, and natalizumab for patients with RRMS who have had an inadequate response to interferon beta or other disease-modifying therapies. The analysis used a Markov model over a 25-year time horizon, from a public-payer perspective. Death was captured separately from other health states. The model also incorporated differential risks of relapses, disease progression, costs, and utility values for each health state. Data on the natural progression of MS were derived primarily from the London, Ontario registry. Data on relative effectiveness of all comparators in terms of disease progression, ARRs and withdrawals were obtained through a mixed treatment comparison (MTC). Health state utility values were based on published UK patient survey, while disutility values were sourced from the published literature. Costs for each state were derived from Canadian data sources. The manufacturer reported that alemtuzumab dominated (i.e., less costly and more effective) all comparator treatments.

CDR identified the following limitations with the manufacturer's pharmacoeconomic model:
- Uncertainty regarding the use of alemtuzumab beyond two years
- Inappropriate inclusion of patients with an EDSS score of 0 in the model
- Inappropriate adjustments to the base mortality inputs
- Overestimated proportion of patients hospitalized following relapse.

These primary limitations were combined to define the CDR base case, which resulted in an ICUR of $31,000 per QALY for alemtuzumab compared with Rebif. CDR identified several other

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parameters of uncertainty (administration and monitoring costs, utility and disutility values, treatment waning, inappropriate use of a mid-cycle correction for alemtuzumab, and the proportion of patients receiving alemtuzumab beyond two years) that were all examined using the CDR base case as a reference. The resulting ICURs ranged from alemtuzumab dominating Rebif to up to $91,000 per QALY for alemtuzumab compared with Rebif, suggesting substantial variability within the model. CDR noted that the ICUR for alemtuzumab compared with Rebif increased substantially with higher EDSS scores at initiation of therapy, particularly EDSS 5 and EDSS 6 (ICUR of approximately $90,000 per QALY and $522,000 per QALY for alemtuzumab compared with Rebif for EDSS 5 and EDSS 6, respectively).

At the submitted price of $[redacted] per 12 mg vial and recommended dosing, the annual cost of alemtuzumab ($[redacted] in the first year; $[redacted] in the second year) is greater than the annual cost of all comparator treatments (annual cost range: $16,241 to $41,062) in the first year, and greater than all except natalizumab ($41,062) in the second year.

Other Discussion Points:

CDEC noted the following:

- In December 2013, the United States Food and Drug Administration (FDA) declined approval for alemtuzumab in RRMS, citing that the manufacturer had not submitted evidence from adequate and well-controlled studies that demonstrate that the benefits outweigh the serious adverse effects. In November 2014, the FDA approved alemtuzumab for the treatment of patients with RRMS after reviewing a resubmission that included additional long-term data.
- Alemtuzumab is listed on the Régie de l'assurance maladie du Québec (RAMQ) drug formulary at a price of $9,970 per 12 mg vial. This represents [redacted] price reduction on the confidential price submitted to CDR.
- Patient groups felt that the dosing schedule was a potential benefit of alemtuzumab. However, the extent to which patients would adhere to recommended follow-up and surveillance testing with this dosing schedule is unconfirmed and a potential source of concern, given risks such as ITP and thyroid abnormalities — which can be detected through routine laboratory monitoring before morbidity or mortality occur.
- Longer-term extension data has become available; however, the methodological limitations, as well as the frequent protocol changes experienced by patients whose data are reported in these studies, leaves room for ongoing uncertainty regarding potential harms of alemtuzumab.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Long-term safety and efficacy require further evaluation.
- With the exception of Rebif, there are no other direct comparisons with other disease-modifying therapies.
- Direct comparison of alemtuzumab to other disease-modifying therapies recommended for patients with inadequate response to interferon or glatiramer for MS is lacking. An MTC was submitted by the manufacturer; however, methodological issues and small sample sizes limit the ability to draw conclusions from this study.

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Regrets:
None

Conflicts of Interest:
None

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CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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