CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

GLATIRAMER ACETATE (GLATECT — PENDOPHARM)
Indication: Relapsing-Remitting Multiple Sclerosis

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that Glatect (subsequent entry glatiramer acetate) be reimbursed in accordance with the Health Canada–approved indication for the treatment of ambulatory patients with relapsing-remitting multiple sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain magnetic resonance imaging (MRI), to decrease the frequency of clinical exacerbations and to reduce the number and volume of active brain lesions identified on MRI scans, if the following criterion and condition are met:

Criterion:
- For use in patients for whom glatiramer acetate is considered to be the most appropriate treatment option.

Condition:
- The cost of treatment with Glatect should provide significant cost savings for jurisdictions compared with the cost of treatment with existing glatiramer acetate products.

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- For use in patients for whom glatiramer acetate is considered to be the most appropriate treatment option.

Condition:

- The cost of treatment with Glatect should provide significant cost savings for jurisdictions compared with the cost of treatment with existing glatiramer acetate products.

Reasons for the Recommendation:

1. In one phase III equivalency trial (GATE GTR001; N = 796) enrolling treatment-naive patients with multiple sclerosis (MS), the ratio of the mean number of gadolinium-enhancing (GdE) lesions on T1-weighted MRIs between months 7 and 9 for patients treated with Glatect versus Copaxone was 1.095 (95% confidence interval [CI], 0.883 to 1.360), falling within the predefined equivalence margin of 0.727 to 1.375.
2. In one phase I controlled, randomized, double-blind, replicate study (GTR002; N = 20), Glatect was shown to have similar tolerability and a similar number of local injection site reactions as Copaxone in healthy volunteers. In addition, the GATE GTR001 trial did not identify any new safety or tolerability concerns in patients treated with Glatect compared to patients treated with Copaxone or placebo.
3. At the manufacturer's submitted price of $37.82 per vial, the cost of Glatect is 15% less than the Ontario Drug Benefit (ODB) Exceptional Access Program (EAP) list price of the originator product, Copaxone; however, the actual cost of Copaxone paid by public drug plans is unknown.

Of Note:

The extension phase of the GATE trial found that patients who were switched from Copaxone to Glatect did not experience any adverse clinical consequences. However, the study did not include a comparator arm; therefore, CDEC considered the assessment of switching patients from Copaxone to Glatect to be hypothesis-generating only. There is insufficient evidence to recommend routine switching of patients already receiving Copaxone treatment. Switching from Copaxone to Glatect could be considered for individual patients after discussion with their treating physician.

Discussion Points:

- CDEC discussed the pre-defined equivalence margin for the primary outcome of the GATE trial. The GATE trial was designed with an equivalence margin based on a 50% preservation of effect of Copaxone versus placebo, which the committee identified as a generous margin. A 50% preservation of effect would equate to approximately a 10% difference in effect of the point estimate for the primary outcome of the GATE trial (T1-GdE lesion count) between Glatect and Copaxone. The clinical expert

consulted for the CADTH Common Drug Review (CDR) review felt that the pre-defined equivalence margin was clinically reasonable.

Background:

Glatect is a subsequent entry glatiramer acetate product based on the originator product, Copaxone. Glatect is a non-biologic complex drug in which all of the related structures of the molecule are active. Therefore, the properties cannot be fully characterized by physicochemical analysis. Glatect has been approved by Health Canada for the treatment of ambulatory patients with RRMS, including patients who have experienced a single demyelinating event and who have lesions typical of multiple sclerosis on brain MRI:

- to decrease the frequency of clinical exacerbations
- to reduce the number and volume of active brain lesions identified on MRI scans.

Glatect is an immunomodulatory agent available as a pre-filled 1 mL syringe containing 20 mg/mL glatiramer acetate to be administered subcutaneously. This indication is identical to the indication of the originator product (Copaxone).

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a review of manufacturer-provided information on the drug similarity of Glatect compared to Copaxone; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

One patient group responded to the CDR call for patient input (Multiple Sclerosis [MS] Society of Canada). Information was collected through a survey posted to the MS Society of Canada website and social media channels from January 23, 2017 to February 5, 2017, and through publicly available information about the impact of MS on patients. The following is a summary of key information provided by the patient group:

- It is common for a treatment to work well in one individual and fail in another, and for a treatment that worked well to become much less effective. Thus, having many treatment options is essential. Treatments also need to be tailored to a patient's symptoms, tolerance, and lifestyle.
- The MS Society believes that the decision to use an originator or a subsequent entry product must be made jointly by people living with MS and their health care providers; individuals should be provided with all relevant information to make an informed choice.
- Patients expressed the desire to have access to a regimen that would allow for less frequent administration.
- The introduction of a cheaper alternative to Copaxone might help patients who experience barriers to access due to cost.

Clinical Trials

The manufacturer provided efficacy data from one pivotal clinical trial in patients with MS and one replicate study in healthy volunteers.

Study GTR001 (GATE; N = 796) was an equivalence randomized controlled clinical trial that evaluated the efficacy of 20 mg/mL daily Glatect versus 20 mg/mL daily Copaxone (reference product) at nine months. The GATE trial was conducted in [redacted] investigational centres [redacted]. The GATE trial enrolled treatment-naive patients with MS with the aim to demonstrate the equivalence of Glatect to Copaxone based on the primary outcome of the total number of GdE lesions during months 7 through 9 on T1-weighted images identified through MRI scans. A pre-defined equivalence margin of 0.727 to 1.375 was specified for the aforementioned primary outcome, based on the preservation of at least 50% of the efficacy of Copaxone compared

to placebo. An additional 15-month open-label extension phase trial (N = 728) was performed at the end of the nine-month double-blind period where patients who were in the placebo group and the Copaxone group switched to Glatect.

Study GTR002 (N = 20) was a phase I controlled, randomized, double-blind replicate study to assess injection site reaction and tolerance of Glatect versus Copaxone in healthy volunteers at one centre in Toronto, Canada. No predefined equivalence margin was identified and no power assessment was conducted for this trial.

Outcomes

CDEC discussed the following outcomes:

- Disease activity — as measured by the total number of T1-GdE lesions identified through MRI scans (i.e., the cumulative number of new and persisting gadolinium-enhancing lesions) during months 7 through 9.
- Relapse — defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination. Relapses were measured by means of annualized relapse rate.
- Disease progression — as informed by the change in the Expended Disability Status Scale (EDSS) from baseline.
- Local injection site reaction — as reported by participants self-administering the injection and by supervising nurses.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The primary outcomes for the trials included in the submission were the total number of T1-GdE lesions identified through MRI scans for the GATE trial (GTR001), and local injection site reactions for the phase I trial (GTR002). Health-related quality of life was not measured in the trials.

Efficacy

Study GTR001 (GATE trial):

The ratio of the total number of T1-GdE lesions in months 7 through 9 between Glatect and Copaxone treated patients was 1.095 (95% CI, 0.883 to 1.360), falling within the predefined equivalence margin of 0.727 to 1.375. The mean number of T1-GdE lesions was [redacted], and [redacted] for Glatect, Copaxone, and placebo groups, respectively. At the end of the open-label extension phase (24 months), the mean number of T1-GdE lesions were [redacted] for the patients that remained on Glatect, switched from Copaxone to Glatect, and switched from placebo to Glatect, respectively.

Changes in the mean EDSS from baseline to nine months were [redacted] for the Glatect, Copaxone, and placebo groups, respectively. At the end of the open-label extension phase (24 months), the mean EDSS changes from baseline were [redacted] for the patients who remained on Glatect, switched from Copaxone to Glatect, and switched from placebo to Glatect, respectively.

At nine months, the annualized relapse rate was 0.31 (95% CI, 0.20 to 0.48), 0.40 (95% CI, 0.26 to 0.62), and 0.38 (95% CI, 0.22 to 0.66) for the Glatect, Copaxone, and placebo groups, respectively. At the end of the open-label extension phase (24 months), the annualized relapse rate was 0.21 (95% CI, 0.13 to 0.34), 0.24 (95% CI, 0.15 to 0.39), and 0.23 (95% CI, 0.12 to 0.42) for patients who remained on Glatect, switched from Copaxone to Glatect, and switched from placebo to Glatect, respectively.

Harms (Safety and Tolerability)

Study GTR001 (GATE trial):

The overall proportion of patients experiencing an adverse event was similar between groups: 180 patients (51.0%) in the Glatect group, 194 patients (54.3%) in the Copaxone group, and 47 patients (56.0%) in the placebo group. The most common adverse events were all related to injection site reactions.

The proportion of patients with serious adverse events was 3.4%, 4.8%, and 2.4% for the Glatect, Copaxone, and placebo groups, respectively.

The proportion of patients with withdrawals due to adverse events was 3.4%, 1.1%, and 2.4% for the Glatect, Copaxone, and placebo groups, respectively.

Study GTR002:

Injection site reactions were recorded in 9.9% of the submitted patient and nurse reports (92 reports out of 925 possible reports) in the Glatect group of healthy volunteers, as opposed to 8.4% reported (78 reports out of 925 possible reports) in the Copaxone group of healthy volunteers.

Cost and Cost-Effectiveness

At $37.82 per 20 mg/mL vial, the annual cost of Glatect ($13,805 per patient) is 15% less than the Ontario Drug Benefit Exceptional Access Program list price of the originator product ($16,241 annually), leading to a savings of $2,436 per patient per year.

CDR identified the following issues for consideration:

- Teva-glatiramer, produced by the same manufacturer as the originator product, has received a Health Canada indication for the treatment of RRMS. If it becomes available, this will be a comparator of interest and, depending on its price, may further reduce the relative attractiveness of the submitted price of Glatect.
- The actual cost paid by Canadian public drug plans for the originator product may be lower than that listed on publicly available formularies, which would reduce the relative attractiveness of the submitted price of the subsequent entry drug.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

June 21, 2017 Meeting

Regrets:

Two CDEC members did not attend the meeting.

Conflicts of Interest:

None