CEDAC FINAL RECOMMENDATION

GLATIRAMER ACETATE
(Copaxone – Teva Pharmaceutical Industries Ltd.)
Indication: Clinically Isolated Syndrome

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that glatiramer not be listed.

Reasons for the Recommendation:
1. Not all patients with clinically isolated syndrome will be subsequently diagnosed with multiple sclerosis. As a result, some patients will be treated with glatiramer, perhaps indefinitely, with no clinical benefit at an annual cost of $15,700.
2. The Committee considered the results of a systematic review that included one randomized controlled trial comparing glatiramer with placebo in patients with clinically isolated syndrome. In this trial, time to diagnosis of clinically definite multiple sclerosis as defined by the Poser criteria was longer for glatiramer compared with placebo but the effect of glatiramer on disability is uncertain.

Of Note:
1. In light of the Committee's reasons for recommendation, drug plans that currently list therapies for clinically isolated syndrome may wish to review their listing criteria.

Background:
Glatiramer has a Health Canada indication for the treatment of patients who have experienced a single demyelinating event accompanied by abnormal magnetic resonance imaging (MRI) scans and are considered to be at risk of developing clinically definite multiple sclerosis (CDMS) after alternate diagnoses are excluded. This is referred to as clinically isolated syndrome (CIS). Glatiramer also has a Health Canada indication for the treatment of relapsing-remitting multiple sclerosis. The focus of this recommendation is CIS.

Glatiramer is available as 20 mg single use vials or prefilled syringes for injection. The recommended dose of glatiramer for CIS is 20 mg given by subcutaneous injection once daily.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review: a systematic review of double-blind randomized controlled trials of glatiramer in patients with CIS and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trial
One manufacturer-sponsored, double-blind, randomized, placebo-controlled trial (PreCISe) of 481 patients with CIS met the inclusion criteria for the CDR systematic review. Patients self-administered daily subcutaneous injections of either glatiramer 20 mg or matching placebo. Patients were enrolled in the study if they had experienced a single clinical neurological attack with unifocal presentation within the last 90 days and had MRI features suggestive of multiple sclerosis (MS), i.e., ≥ two T2 lesions; these CIS patients are considered to be at high risk for the development of MS.

The double-blind, randomized, placebo-controlled phase of the study was designed to last a maximum of three years with an additional two-year uncontrolled, open-label extension phase (total study duration five years). Based on the results of a preplanned interim analysis and on the recommendation of the data monitoring committee, the placebo-controlled phase of the trial was stopped early and all patients were switched to open-label glatiramer. Follow-up of these patients is ongoing. At the time of the interim analysis, 226 patients, 47% of the study population (96 receiving glatiramer and 130 receiving placebo) had completed the placebo-controlled phase, either because of conversion to CDMS or because of completing three years of treatment. The eventual outcome of a large proportion of patients is unknown because the trial was stopped early based on the interim analysis results.

Withdrawals were higher in the glatiramer group compared with placebo (16% versus 10%). Missing data were handled using a last observation carried forward approach, which may have biased the results. Although the trial was blinded, glatiramer is commonly associated with injection site reactions, which may have unblinded investigators and patients; the effectiveness of blinding in PreCISe was not evaluated.

Outcomes
The primary outcome of PreCISe was the time to conversion to CDMS diagnosed by the Poser criteria, defined as the time from the date of randomization to the date of a second clinical neurological event consistent with the definition of CDMS.

In addition, the Committee discussed the following outcomes included in the CDR systematic review: proportion of patients progressing to CDMS, changes in disability and adverse events.

Disability, as measured by the Expanded Disability Status Scale (EDSS), was not an a priori outcome of PreCISe and data regarding disability associated with cognitive impairment or fatigue was not available. In addition, quality of life and hospitalizations were not measured in the PreCISe trial.

Results

Efficacy or Effectiveness

- The primary outcome of time to conversion to CDMS was statistically significantly longer in the glatiramer group compared with placebo: 722 days versus 336 days, (hazard ratio 0.55, 95% confidence interval [CI]: 0.40 to 0.77, P = 0.0005). At the time of the interim analysis, less than 50% of glatiramer-treated patients had converted to CDMS, therefore the eventual outcome of a large proportion of patients is unknown.
- A statistically significantly smaller proportion of glatiramer patients converted to CDMS compared with placebo patients (25% versus 43%, relative risk 0.58, 95% CI: 0.44 to 0.75, P < 0.0001). Once these patients converted to CDMS, they entered an open-label extension.
- In a manufacturer's post-hoc analysis, time to disability was defined as the time to a worsening of EDSS scores by at least one point and sustained over two consecutive measurements at least three or six months apart. Acknowledging the limitations associated with results generated by post-hoc analyses, it was observed that time to disability was similar between glatiramer and placebo patients. In addition, 20% of glatiramer patients and 19% of placebo patients had a one point worsening in EDSS over a three month period. EDSS scores primarily reflect disability associated with motor function and mobility.

Harms (Safety and Tolerability)

- Serious adverse events and total adverse events were similar between glatiramer and placebo groups. The most common adverse events associated with glatiramer were injection site reactions, dyspnea and flushing.
- There were significantly more patients receiving glatiramer compared with placebo who reported erythema, induration, irritation, pain, pruritis and swelling associated with injection site reactions.
- Withdrawals due to adverse events were greater in the glatiramer group compared with placebo (6% versus 2%, P = 0.03).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis based on the assumption of similar clinical efficacy, safety and tolerability in the treatment of CIS for glatiramer, interferon beta-1a (Avonex) and interferon beta-1b (Betaseron). There are no randomized controlled trials comparing interferons with glatiramer and the manufacturer's analysis was based on an indirect comparison of placebo-controlled trials for each of these treatments. The weekly cost of treatment with glatiramer is $302, which is less than comparator treatments: interferon beta-1a (Avonex, $374; Rebif, $374 to $456) and interferon beta-1b (Betaseron, $394).

Given that the Committee considered the effect of glatiramer on disability uncertain, the Committee could not determine the cost-effectiveness of glatiramer in CIS.

Other Discussion Points:

- The relevance of time to CDMS diagnosis as an outcome was discussed. The Committee felt that the impact of treatment on long-term disability was a more important outcome measure. It is unknown if delaying a second clinical attack, as required for diagnosis of CDMS by the Poser criteria, has any long-term effect on disability.

- The Committee noted that there are long-term studies evaluating interferons in the treatment of CIS such as BENEFIT and CHAMP/CHAMPIONS that have reported up to five years of data. These studies have found no benefit of early treatment initiation versus delayed treatment initiation on disability, as measured by the EDSS.
- The Committee discussed the different criteria used to diagnose MS. Using the Poser criteria the diagnosis is based on two separate clinical attacks, whereas using the revised McDonald criteria, the diagnosis is most often based on one clinical attack and changes in MRI findings at a second point in time. The revised McDonald criteria would result in an earlier diagnosis of MS than with the Poser criteria. In Canada, a large proportion of patients will likely be assessed and followed in a centre with MRI access, therefore the McDonald criteria are more clinically relevant.
- Not all patients diagnosed with CIS are subsequently diagnosed with MS. Therefore, there are patients who will be treated for CIS, perhaps indefinitely, with no benefit. Estimates of the ten-year risk of conversion to CDMS for patients with CIS and abnormal MRI findings range from 56% to 83%.

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating:
September 16th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Michael Evans, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Kelly Zarnke.

November 18th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
September 16th, 2009: Dr. Yvonne Shevchuk.

November 18th, 2009: Dr. Michael Allan, Dr. Lindsay Nicolle.

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote.

About This Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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