CDEC FINAL RECOMMENDATION

TERIFLUNOMIDE
(Aubagio — Genzyme Canada)
Indication: Relapsing-Remitting Multiple Sclerosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that teriflunomide not be listed at the submitted price.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) (TOWER and TEMSO) demonstrated that the annualized relapse rate was lower with teriflunomide compared with placebo for patients with relapsing-remitting multiple sclerosis (RRMS) and one RCT (TENERE) demonstrated no statistically significant difference in the annualized relapse rate between teriflunomide and interferon beta-1a.
2. At the submitted price, teriflunomide ($[redacted] per year) is more costly than glatiramer acetate ($16,241 per year) and interferon beta-1b (Extavia) ($18,133 per year). CDEC concluded that, without evidence demonstrating superior clinical benefit with teriflunomide compared with other available treatments for RRMS, a higher cost for teriflunomide is not justified.

Of Note:
Based on a review of the clinical evidence, CDEC noted that a reduction in price would increase the likelihood of a recommendation to list or list with clinical criteria and/or conditions.

Background:
Teriflunomide is an immunomodulatory drug with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, required for the de novo pyrimidine synthesis. Teriflunomide is the primary active metabolite of leflunomide, a drug which is indicated for the treatment of rheumatoid arthritis. Teriflunomide is indicated for use as monotherapy for the treatment of patients with RRMS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Teriflunomide is available as a 14 mg film-coated tablet. The recommended dose in the product monograph is 14 mg orally once daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of teriflunomide, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of patient group-submitted information about outcomes and issues important to patients.

Patient Input Information
The following is a summary of key information provided by the one patient group that responded to the CDR call for patient input:

- People living with multiple sclerosis (MS) indicated that the following common symptoms have a major impact on their lives: difficulty with walking and coordination of arms or legs, fatigue, loss of vision, numbness or tingling, memory or attention problems, and pain. They noted that MS has a significant impact on their ability to work, creates financial and emotional burdens, and negatively affects their family and social lives.
- Current MS therapies reduce the frequency and severity of relapses and possibly slow the progression of disability; however, they are limited by their high cost, side effects, and, commonly, by their related need for injections or infusions.
- People living with MS place great value on oral therapies, which could potentially improve their quality of life as well as provide additional treatment choices. Oral drug therapy would offer independence in taking medication for people who are not able to self-inject current treatments, which can be an issue in a disease that can result in numbness and lack of coordination. Patient groups believe that this will help improve compliance.

Clinical Trials
Four randomized, multicenter, parallel group, superiority trials were included in the CDR systematic review. Patients were included in the trials if they had MS with a relapsing course and met the McDonald 2005 criteria or Poser criteria. TENERE (N = 324) was an active-controlled, rater-blinded trial and patients were randomized to either one of two teriflunomide doses (7 mg or 14 mg once daily) or to interferon beta-1a (Rebif) 44 mcg three times per week. TEMSO (N = 1,088), TOWER (N = 1,169), and study 2001 (N = 179) were double-blind, placebo-controlled trials and patients were randomized to either one of two teriflunomide doses (7 mg or 14 mg once daily) or placebo. In TENERE and in TOWER, patients were treated for a minimum of 48 weeks to a maximum of 118 weeks or 160 weeks, respectively. In TEMSO and in study 2001, patients were treated for 108 weeks and 36 weeks, respectively.

Based on the recommended dosing for teriflunomide, CDEC focused its discussion on the results reported for the 14 mg once daily dosing regimen.

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

- Disability progression — defined as an increase in the Expanded Disability Status Scale (EDSS) from baseline of ≥ 1-point (baseline EDSS ≤ 5.5) or ≥ 0.5-point (baseline EDSS > 5.5) that was persistent for at least 12 weeks. The 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.

- Relapse — defined as appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (stable for at least 30 days) that persisted for a minimum of 24 hours without fever.
- Multiple Sclerosis Functional Composite (MSFC) — used to assess ambulation, upper limb dexterity, and cognition using the following: the Timed 25-Foot Walk Test, Nine-Hole Peg Test, and three-second Paced Auditory Serial Addition Test.
- Health-related quality of life — assessed using the SF-36 Health Survey, the European Quality of Life-5 Dimensions (EQ-5D) questionnaire (visual analogue scale and index scores), the Fatigue Impact Scale (FIS), and the Multiple Sclerosis Quality of Life instrument (MSQOL-54).
- Magnetic resonance imaging (MRI) — used to assess changes in the number and volume of lesions.

The primary efficacy end point in TENERE was time to failure (time to occurrence of first relapse or treatment discontinuation). In TOWER and TEMSO, the primary efficacy end point was the annualized relapse rate. In study 2001, the primary efficacy end point was the number of unique active lesions per MRI scan.

Efficacy

Active-controlled trial

- In TENERE, there was no statistically significant difference in the adjusted annualized relapse rate between teriflunomide and interferon beta-1a (rate ratio 1.2 [95% confidence interval [CI], 0.6 to 2.3]).
- There was no statistically significant between-treatment difference in the time to failure (hazard ratio 0.86 [95% CI: 0.56 to 1.31]).
- There were no statistically significant between-treatment differences in change from baseline in FIS scores.

Placebo-controlled trials

- The adjusted annualized relapse rate was statistically significantly lower with teriflunomide compared with placebo in both TOWER and TEMSO with rate ratios of 0.64 (95% CI: 0.51 to 0.79) and 0.69 (95% CI: 0.55 to 0.85), respectively.
- Time to disability progression sustained for 24 weeks was not statistically significantly different between placebo and teriflunomide in TOWER (hazard ratio 0.84 [95% CI: 0.53 to 1.33] and TEMSO (hazard ratio 0.75 [95% CI: 0.51 to 1.11]).
- For all other outcomes in TOWER and TEMSO, statistical significance was not addressed in the CDR review because they fell below a non-significant parameter in the hierarchical chain to address multiplicity.
- In TOWER and TEMSO, teriflunomide treatment effects for the outcomes of annualized relapse rate and sustained disability progression were consistent across two subgroups: patients with or without prior use of disease-modifying treatments in last two years; and patients with EDSS ≤ 3.5 or > 3.5.
- In study 2001, the number of new T2 lesions for the treatment period was statistically significantly lower with teriflunomide (0.42 ± 0.19 standard error) compared with placebo (1.07 ± 0.19 standard error, $P = 0.008$) but not for newly enlarging T2 lesions ($P = 0.09$).

- [redacted].

Harms (Safety and Tolerability)

- In TENERE, 5.5% of patients experienced a serious adverse event with teriflunomide compared with 6.9% for the interferon beta-1a group. In the three placebo-controlled trials, the proportion of patients with serious adverse events ranged from 11.9% to 15.9% with teriflunomide and from 11.5% to 12.8% with placebo.
- In TENERE, 21.8% of patients in the interferon beta-1a group withdrew compared with 10.9% of patients in the teriflunomide group. In the three placebo-controlled trials, withdrawals due to adverse events were more common with teriflunomide, ranging from 10.9% to 15.6% compared with 6.2% to 8.1% for the placebo groups. The most common reasons for withdrawing from teriflunomide included alopecia/hair-thinning, increased alanine aminotransferase, and neutropenia.
- Common adverse events with teriflunomide included diarrhea (20.9%), nasopharyngitis (20.0%), and headache (15.5%). Up to 20% of patients reported alopecia/hair-thinning with teriflunomide 14 mg compared with 1% with interferon beta-1a, and < 10% with placebo.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis to assess teriflunomide (14 mg once daily) in patients with relapsing forms of MS with an EDSS score of ≤ 5.5 who are treatment-naive, or those requiring a first switch to another therapy due to intolerance. The primary analysis compared teriflunomide with interferon beta-1a (Avonex), interferon beta-1a (Rebif), glatiramer acetate, and dimethyl fumarate using a Markov model of disease progression, where patients can progress through EDSS levels and move from RRMS to secondary progressive MS (SPMS), and death. A 20-year time horizon was considered, with cycle lengths of one-year. Death was captured separately to allow for an increasing risk of mortality by age and EDSS level. The model incorporated differential risks of relapses, costs, and utility values for each EDSS level. Data on the natural progression of MS were derived primarily from the London Ontario registry, supplemented by data from the placebo groups of the TEMSO and TOWER trials. Data on relative effectiveness of all comparators in terms of disease progression, annualized relapse rates, and withdrawals were obtained through an unpublished mixed treatment comparison (MTC) restricted to studies published since 2000 with 80% of patients with RRMS. Utility values and costs for each state were derived from Canadian data sources. The manufacturer reported that teriflunomide dominates Rebif and Avonex (i.e., less costly and associated with greater clinical benefits), and has an incremental cost-utility ratio (ICUR) of $33 per quality-adjusted life-year (QALY) compared with glatiramer acetate. Dimethyl fumarate was reported to be more costly, but associated with greater QALYs compared with teriflunomide.

The following key limitations were identified with the manufacturer's model:

- The MTC submitted by the manufacturer was restricted to trials published after 2000 and only assessed sustained accumulation of disability at three months, which might have biased the results in favour of teriflunomide. CDR re-analysis used estimates from the CADTH therapeutic review on drug therapies for RRMS.
- The utility values used by the manufacturer were much lower than those found in other published studies. In the CDR re-analysis alternate utility values were considered.
- The manufacturer assumed that the effectiveness of treatment would be maintained over the patient's lifetime, although the duration of follow-up in the TEMSO clinical trial was

108 weeks. The impact of waning of treatment effect could not be explored in the manufacturer's model.
- Given the transient nature of the reported adverse events, CDR performed a re-analysis in which the associated costs and disutilities of adverse events were excluded.
- The health care costs by EDSS state and for relapse that were used by the manufacturer ignored the possibility that patients with a hospitalized relapse could also have a relapse not requiring hospitalization. CDR re-analyses were conducted using alternative cost estimates.
- Mortality by EDSS state was derived from a study by Sadovnick et al., which presented mortality rates for three grouped EDSS categories: 0 to 3.5, 4 to 7, and 7.5 to 9. The manufacturer applied different mortality rates for each individual EDSS state. CDR re-analysis adopted the actual data from Sadovnick et al.
- The manufacturer presented different withdrawal rates between treatments. As treatments became more cost-effective when associated with a higher withdrawal rate, CDR undertook a re-analysis assuming a constant withdrawal rate across all treatments (17% per annum as per teriflunomide 14 mg).

Undertaking re-analyses based on the alternate assumptions, CDR found the following:
- teriflunomide continues to dominate Rebif and Avonex (i.e., less costly and more QALYs)
- teriflunomide has an ICUR of $409,175 compared with glatiramer acetate
- dimethyl fumarate is more effective, but more costly than teriflunomide (ICUR of $10,030).

The interpretation of results did not vary when stratifying by EDSS states.

At the submitted price of $[redacted] per 14 mg tablet, the annual cost of teriflunomide is $[redacted], which is more costly than glatiramer acetate ($16,241 per year) and interferon beta-1b (Extavia) ($18,133 per year), but less costly than other comparator drugs, based on current list prices.

Other Discussion Points:
CDEC noted the following:
- The "Of Note" comment in the CDEC recommendation for dimethyl fumarate, another oral treatment for RRMS, as well as the CADTH therapeutic review for RRMS had the following statement: "*At the submitted price, dimethyl fumarate is not a cost-effective option for initial treatment of RRMS.*"
- It was unclear if patients included in the trials were treatment-experienced. Although < 25% of patients reported prior use of disease-modifying treatments in the last two years, there was no information on lifetime treatment experience.
- Orally administered treatments are often considered to be more convenient for patients than those that require intravenous or subcutaneous administration.
- The MTC was limited by the heterogeneity of the included trials.
- There was no statistically significant difference between teriflunomide and interferon beta-1a in TENERE; however, this trial was not designed to assess equivalence or non-inferiority between these two active treatments. In addition, there was a very wide CI for the annual relapse rate, suggesting that this study might have been underpowered to demonstrate a difference between teriflunomide and interferon beta-1a.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- There are no long-term outcome data on disability progression from RCTs for teriflunomide or other drugs for the treatment of RRMS.
- The long-term safety profile of teriflunomide in the treatment of MS requires further evaluation.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

May 21, 2014 Meeting
Regrets:
None

Conflicts of Interest:
None

About this Document:
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 in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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