CDEC FINAL RECOMMENDATION

FINGOLIMOD
(Gilenya – Novartis Pharmaceuticals Canada Inc.)
Indication: Multiple Sclerosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that fingolimod be listed for the treatment of patients with relapsing remitting multiple sclerosis (MS) who meet all of the following criteria:

- Failure to respond to full and adequate courses of at least one interferon beta formulation and glatiramer acetate, or contraindications to these therapies
- Two or more disabling relapses in the previous year
- Significant increase in T2 lesion load compared with that from a previous magnetic resonance imaging (MRI) scan, or at least one gadolinium-enhancing lesion.

The Committee further recommends that fingolimod treatment be stopped in patients with relapsing remitting MS who meet either of the following criteria:

- failure to achieve at least a 50% reduction from baseline in the average annual relapse rate after two years
- attainment of an Expanded Disability Status Scale (EDSS) score of greater than 5.0.

Reasons for the Recommendation:

1. Based on one double-blind randomized controlled trial (RCT), TRANSFORMS, the Committee considered fingolimod and interferon beta-1a to have similar efficacy. Although the differences in annualized relapse rates and disability scores were statistically significant in favour of fingolimod, the observed differences were small. In addition, no between-treatment differences in quality of life were demonstrated.
2. At recommended doses, the yearly cost of fingolimod ($30,992) is more expensive than glatiramer ($15,704), interferon beta-1a ($18,928 to $23,036), and interferon beta-1b ($18,096).
3. The Committee recognized patient group input that pointed to the need for additional treatment options in MS.
4. The Committee considered continued use of a high-cost agent to be unwarranted in the absence of substantial sustained clinical benefit.

Of Note:
Based on a review of the clinical evidence, the Committee felt that a reduced price similar to that of interferon products would increase the likelihood of a recommendation with less restrictive criteria.

Background:
Fingolimod has a Health Canada indication as monotherapy for the treatment of patients with the relapsing remitting form of MS, to reduce the frequency of clinical exacerbations and to delay the progression of physical disability. According to the Health Canada indication, fingolimod is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for MS.

Fingolimod is a sphingosine-1 receptor modulator. It modulates trafficking of T-cells in the central nervous system, and thus has an immunosuppressive effect. It is available as a 0.5 mg oral capsule and the Health Canada recommended dose is 0.5 mg once daily.

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

Clinical Trials
The systematic review included two double-blind RCTs of adult patients with relapsing remitting MS, as defined by the 2005 revised McDonald criteria. The TRANSFORMS trial (N = 1,292) was a 12-month multicentre trial that compared two doses of fingolimod (0.5 mg and 1.25 mg once daily) with interferon beta-1a 30 mcg intramuscularly once weekly. The FREEDOMS trial (N = 1,272) was a 24-month multicentre trial that compared two doses of fingolimod (0.5 mg and 1.25 mg once daily) with placebo. Both trials enrolled patients who were treatment naive or previously treated, with at least one documented relapse during the previous year or two documented relapses during the previous two years prior to randomization, and an EDSS score of 0 to 5.5.

Patients in both trials were similar in terms of mean number of relapses in the past year (1.5 in both trials) and mean EDSS score (2.2 and 2.4 for TRANSFORMS and FREEDOMS, respectively). The percentage of patients who completed the trial was 89% for TRANSFORMS and 81% for FREEDOMS.

Limitations of the trials include the heterogeneity of enrolled patients with regard to baseline disability scores and the possibility of compromised blinding in the TRANSFORMS trial, due to the flu-like symptoms experienced by patients in the interferon treatment group. The Committee considered results from a network meta-analysis; *[unpublished results of this meta-analysis are not being disclosed because the manufacturer requested that this confidential information be removed pursuant to the CDR Confidentiality Guidelines].* The Committee also noted the inherent limitations of the primary outcome of both studies (annualized relapse rate) in predicting the long-term outcomes of a disease that evolves over many years. No double-blind RCTs were identified that compared fingolimod with other interferon beta-1 products, glatiramer or natalizumab.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: annualized relapse rate, percentage of relapse-free patients, disability, fatigue, quality of life, and MRI findings (new or newly enlarged T2 lesions). The primary outcome of both TRANSFORMS and FREEDOMS was the annualized relapse rate.

Disability was assessed based on the EDSS and the Multiple Sclerosis Functional Composite (MSFC). The EDSS is an ordinal scale, composed of eight functional systems (plus "other"), with the total score ranging from 0 to 10, higher numbers indicating worse disability. The MSFC includes tests of ambulation, arm function, and cognition; findings are reported as the mean of the three components as z-scores.

Quality of life was assessed in all patients in the TRANSFORMS trial using the European Quality of Life — 5 Dimensions (EQ-5D). Fatigue was assessed for only a proportion of the patients in TRANSFORMS using the modified fatigue impact scale. Measures of quality of life and fatigue were not included in FREEDOMS.

Results

The Committee focused its discussion on results of the approved dose of fingolimod. Thus, the results described below are for fingolimod 0.5 mg daily, unless otherwise noted.

Efficacy

- The annualized relapse rate was statistically significantly lower for fingolimod compared with both interferon (0.16 versus 0.33) and placebo (0.18 versus 0.40). In a post hoc analysis, these findings were consistent for both treatment-experienced and treatment-naive subgroups in the TRANSFORMS and FREEDOMS trials. The percentage of patients who were relapse free was statistically significantly greater for fingolimod compared with interferon in TRANSFORMS (83% versus 69%) and compared with placebo in FREEDOMS (70% versus 46%).
- Improvements in the MSFC z-scores were statistically significantly greater for fingolimod compared with both interferon and placebo; however, the Committee did not consider the differences to be clinically meaningful. A statistically significant improvement in the EDSS score was observed for fingolimod compared with placebo only; the Committee did not consider the difference to be clinically meaningful.
- The percentage of patients who were free from disability progression was statistically significantly different between fingolimod and placebo (88% versus 81%, respectively), but not between fingolimod and interferon (94% versus 92%, respectively).
- There was no statistically significant difference between fingolimod and interferon in terms of fatigue or quality of life.
- Compared with interferon, there were significantly fewer new or newly enlarged T2 lesions with fingolimod 0.5 mg (1.7 versus 2.6, P = 0.004). In FREEDOMS, there were significantly fewer new or newly enlarged T2 lesions versus placebo with fingolimod 0.5 mg (2.5 versus 9.8, P < 0.001).

Harms (Safety and Tolerability)

- The incidence of serious adverse events and withdrawal due to adverse events was not statistically significantly different between fingolimod 0.5 mg and interferon, or between fingolimod 0.5 mg and placebo.
- There were significantly fewer patients with an adverse event in the fingolimod 0.5 mg group versus interferon (86% versus 92%, P = 0.009). Adverse events commonly associated with interferons, such as flu-like illness, occurred in a higher percentage of interferon patients than fingolimod patients (37% versus 4%). In FREEDOMS, there was no difference in the incidence of adverse events between fingolimod 0.5 mg and placebo (94% versus 93%, P = 0.30).
- Two patients randomized to fingolimod 1.25 mg in TRANSFORMS died due to herpes infection. The Committee noted other potential safety concerns with fingolimod, including cardiovascular events (including atrioventricular block and hypertension) and elevated liver enzymes.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing fingolimod with interferon beta-1a both for (i) patients with active relapsing remitting MS *[the confidential operational definition of this subgroup is being removed as requested by the manufacturer]*, and (ii) patients who were non-responders *[the confidential operational definition of this subgroup is being removed as requested by the manufacturer]*. Efficacy data for fingolimod, in terms of disability progression and annualized relapse rate, were derived from a sub-group analysis from FREEDOMS; efficacy data for interferon were derived from a network meta-analysis of intention to treat populations. Discontinuation rates for fingolimod and interferon beta-1a were derived from an observational study and network meta-analysis. Progression of MS over a 25-year time horizon was based on a patient's EDSS level and patient's current therapy. Health state utility values used to calculate quality-adjusted life-years (QALYs) for EDSS levels in the model were derived from a single United Kingdom study. Health care costs for EDSS levels were derived from the TRIBUNE study. The model also accounted for transitory relapses, where a fixed cost and utility decrement were assigned to all relapses irrespective of nature, severity, and duration. Costs and clinical benefits were discounted at a rate of 5% per annum. The manufacturer reports that fingolimod compared with interferon results in a cost per QALY of $16,135 in patients who have active relapsing remitting MS and $44,136 per QALY in patients who are non-responders.

CDR identified a number of limitations with the manufacturer's analyses, which could affect the estimates of cost-effectiveness. The cost per QALY estimates were less favourable when compared with other active comparators (glatiramer or other interferon) or best supportive care; cost per QALY estimates ranged from $48,698 to $337,381. There was uncertainty regarding a number of input parameters, including utility values associated with EDSS levels, treatment effects of fingolimod on relapses and disability progression and the duration of benefit, and transition probabilities used to estimate disease progression. When more conservative assumptions regarding model parameters were applied and other comparators were considered by CDR, the incremental cost per QALY estimates for fingolimod were higher than those submitted by the manufacturer (> $100,000).

At recommended doses, the yearly cost of fingolimod ($30,992) is similar to natalizumab ($33,020) but more expensive than glatiramer ($15,704), interferon beta-1a ($18,928 to $23,036), and interferon beta-1b ($18,096).

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

- The following symptoms were identified as having a major impact on the lives of patients with MS: fatigue, difficulty in walking, memory or attention problems, numbness or tingling, pain, bladder problems, and depression.
- Patients identified a number of side effects with current therapies (interferon products, glatiramer, and natalizumab) that included injection site reactions, fatigue, headache, and sore muscles and joints. Although these side effects did not regularly affect the use of therapy, patients expressed the desire for treatment options with fewer side effects. Fatigue and injection site reactions were identified as the most common side effects that might affect compliance.
- Patients expect the first oral agent for MS (fingolimod) to improve their quality of life by eliminating the need for injections, reducing the severity and frequency of relapses, and resulting in fewer adverse effects.

Other Discussion Points:

- While the two fatalities due to herpes infections were reported in patients receiving 1.25 mg of fingolimod daily (non-approved dose), the Committee noted that there are still limited safety data available for fingolimod 0.5 mg daily.
- The Committee noted that MS patients comprise a heterogeneous population and that MS is characterized by a widely varying clinical course.
- The Committee recognized that oral treatment may be perceived as being more convenient for patients; however, the Committee regarded the current price premium for fingolimod to be excessive, given its similar clinical efficacy to interferon.

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. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, Dr. Adil Virani.

October 19, 2011 Meeting

Regrets:
Two CDEC members did not attend

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. 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 Final CDEC Recommendation 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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