Canadian Drug Expert Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Gilenya, which is also called fingolimod, be listed by Canada's publicly funded drug plans for the treatment of patients with relapsing remitting multiple sclerosis (MS) who meet all of the following criteria:

- Failure to respond to full and appropriately dosed courses of at least one interferon beta medication (e.g., Avonex, Rebif) and glatiramer acetate (also called Copaxone), or have contraindications to these therapies (are unable to take the drugs for medical reasons)
- Two or more disabling relapses (attacks) in the previous year
- An important increase in the number of T2 lesions (sign of inflammation and tissue damage) on a magnetic resonance imaging (MRI) scan compared with an earlier MRI scan, or at least one gadolinium-enhancing lesion (sign of ongoing active inflammation and tissue injury).

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

- Failure to have a 50% or greater decrease in the number of relapses per year (compared with the amount before the start of treatment) after two years
- Reach an Expanded Disability Status Scale (EDSS) score of greater than 5.0.

Reasons for the Recommendation:

1. Based on one medical study (TRANSFORMS), the Committee considered the effectiveness of Gilenya and interferon beta-1a to be similar. Although study results, based on the number of relapses per year and disability scores, appeared better for patients in the Gilenya group, the differences seen between the treatments were small. In addition, no difference in quality of life was seen between Gilenya and interferon beta-1a.
2. At recommended doses, the yearly cost of Gilenya ($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 an expensive treatment to not be reasonable unless an important and continuing benefit of treatment was seen.

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

Background:
Gilenya is a sphingosine-1 receptor modulator. Gilenya can alter the way the body's immune system works. Gilenya lowers the number of white blood cells (lymphocytes) in the blood by preventing them from moving freely within the body. In MS, when lymphocytes reach the brain and spinal cord, they are thought to cause the inflammation that contributes to loss of myelin. Gilenya may keep these cells from reaching the brain and spinal cord. However, as lymphocytes are also important for the body's normal ability to fight infections, an important side effect of Gilenya is that the patient may get infections more easily because there are fewer cells available in the blood to fight infections.

Gilenya is approved by Health Canada as monotherapy (not to be used in combination with other MS treatments) for the treatment of patients with the relapsing and remitting form of MS, to reduce the frequency of clinical exacerbations (worsenings) and to delay the progression of physical disability. According to the Health Canada indication, Gilenya is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for MS.

Gilenya 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:
To make its decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Gilenya and a review of economic information prepared by the manufacturer of Gilenya. In addition, the Committee considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
The systematic review included two medical studies of patients with relapsing remitting MS, as defined by the 2005 revised McDonald criteria. The TRANSFORMS study, with 1,292 patients, was a 12-month study in more than one location that compared two doses of Gilenya (0.5 mg and 1.25 mg once daily) with interferon beta-1a injection (30 mcg given into the muscle once weekly). The FREEDOMS study, with 1,272 patients, was a 24-month study in more than one location that compared two doses of Gilenya (0.5 mg and 1.25 mg once daily) with placebo (a pill containing no active medication). Both studies included patients who had already received a treatment for MS as well as those who had not. Patients in both trials were required to have had at least one relapse during the previous year or two relapses during the previous two years, and an EDSS score of 0 to 5.5.

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

There were some drawbacks with the studies. For example, not all the patients in the studies were at a similar point in their disease (based on the wide range of disability scores reported) and there was a possibility that patients given interferon beta-1a might have guessed what treatment they were receiving if they developed flulike symptoms, which are common with interferon treatments. In addition, the Committee considered results from an analysis of a number of different studies of MS drugs; *[unpublished results of this analysis are not being provided because the manufacturer requested that this confidential information be removed, in agreement with the CDR Confidentiality Guidelines]*. The Committee also noted that the main result of both studies (yearly relapse rate) may not be that useful in predicting the long-term outcomes of a disease that evolves over many years. No medical studies comparing Gilenya with other interferon beta-1 products, glatiramer acetate, or natalizumab (also called Tysabri) were found.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: yearly relapse rate, percentage of patients without relapse, disability, fatigue (tiredness), quality of life, and MRI results (new or newly growing T2 lesions). The main result of both TRANSFORMS and FREEDOMS was the yearly relapse rate.

Disability was measured based on the EDSS and the Multiple Sclerosis Functional Composite (MSFC). The EDSS is a numbered scale made up of eight functional systems (plus “other”), with the total score ranging from 0 to 10, with higher numbers indicating worse disability. The MSFC includes tests of walking, arm function, and thinking; results are reported as the average of the three tests translated into z-scores.

Quality of life was measured in all patients in the TRANSFORMS study, using the European Quality of Life – 5 Dimensions (EQ-5D) questionnaire. Fatigue was measured 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 Gilenya. Thus, results described below are for Gilenya 0.5 mg daily, unless otherwise noted.

Efficacy or Effectiveness

- The yearly relapse rate was lower for Gilenya compared with interferon (0.16 versus 0.33) and compared with placebo (0.18 versus 0.40). Similar results were seen both in patients who had already received a treatment for MS and those who had not, in the TRANSFORMS and FREEDOMS studies. The percentage of patients who did not have any relapses during the study was greater for Gilenya compared with interferon in the TRANSFORMS study (83% versus 69%) and compared with placebo in the FREEDOMS study (70% versus 46%).
- There was greater improvement in the MSFC z-scores for Gilenya compared with both interferon and placebo; however, the Committee did not consider the differences to be

important for patients. An improvement in the EDSS score was seen for Gilenya compared with placebo only; however, the Committee did not consider the difference to be important for patients.

- The percentage of patients who did not have worsening of their disability was greater for Gilenya compared with placebo (88% versus 81%, respectively), but was about the same for Gilenya compared with interferon (94% versus 92%, respectively).
- There was no difference between Gilenya and interferon in terms of patients' fatigue or quality of life.
- Compared with interferon, the average number of new or growing T2 lesions was lower for Gilenya (1.7 versus 2.6). In FREEDOMS, the average number of new or growing T2 lesions was lower for Gilenya compared with placebo (2.5 versus 9.8).

Harms (Safety and Tolerability)

- The percentage of patients with serious side effects and the percentage of patients who stopped taking part in the study because of side effects was similar between Gilenya and interferon, and between Gilenya and placebo.
- The percentage of patients who had a side effect was lower for Gilenya compared with interferon (86% versus 92%) in the TRANSFORMS study. Side effects usually linked to interferons, such as flulike illness, occurred in a higher percentage of interferon patients than Gilenya patients (37% versus 4%). In the FREEDOMS study, there was no real difference in the percentage of patients who had a side effect between Gilenya and placebo (94% versus 93%).
- Two patients on Gilenya 1.25 mg in TRANSFORMS died due to herpes infection. The Committee noted other potential safety concerns with Gilenya, including cardiovascular events (heart and blood vessel problems), such as high blood pressure and atrioventricular block (where the electrical current does not flow through the heart properly), as well as higher liver enzymes in the blood.

Cost and Cost-Effectiveness

The manufacturer submitted economic information comparing the cost-effectiveness of Gilenya with interferon beta-1a in two different patient groups:

- Patients with active relapsing remitting MS *[confidential information about how the manufacturer defined this type of patient is being removed as requested by the manufacturer]*, and
- Patients who had not responded to previous treatment *[confidential information about how the manufacturer defined this type of patient is being removed as requested by the manufacturer]*.

Results for Gilenya, in terms of worsening disability and yearly relapse rate, were taken from an analysis of the FREEDOMS study, while results for these outcomes for interferon were taken from an analysis of various studies. Discontinuation rates for Gilenya and interferon beta-1a were taken from a number of studies.

The manufacturer estimated the cost-effectiveness of Gilenya over a 25-year time frame by linking patients' EDSS levels to medical costs and quality of life. In the manufacturer's analysis, every relapse (regardless of its severity and duration) was assumed to have the same medical cost and to result in the same reduction in quality of life.

CDR found a number of potential issues with the manufacturer's analyses that could affect their estimates of cost-effectiveness. The cost-effectiveness of Gilenya was not as good when Gilenya was compared with other treatments such as glatiramer or other interferons or even best supportive care (treatment other than with MS medication). In addition, it is uncertain whether a number of assumptions used in the manufacturer's economic analysis are true. This includes assumptions about the link between EDSS levels and quality of life, effects of Gilenya on relapses and disability progression, the duration of the benefit from Gilenya, and estimates of disease progression. When stricter assumptions were made, Gilenya did not appear as cost-effective as was suggested by the manufacturer's analysis.

At recommended doses, the yearly cost of Gilenya ($30,992) is similar to that of 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 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 (rash and swelling around the site of the injection), fatigue, headache, and sore muscles and joints. Although these side effects did not regularly affect the use of therapy, patients said they would like treatment options with fewer side effects. Fatigue and injection site reactions were identified as the most common side effects that might affect whether patients take the medication regularly as prescribed.
- Patients expect the first oral medication for MS (Gilenya) to improve their quality of life by taking away the need for injections, decreasing the severity and frequency of relapses, and by causing fewer side effects.

Other Discussion Points:

- While the two deaths due to herpes infections were reported in patients receiving 1.25 mg of Gilenya daily (not an approved dose in Canada), the Committee noted that there is still not much safety data available for Gilenya 0.5 mg daily.
- The Committee noted that MS patients are a diverse population and that MS is a disease that may have a very different pattern in different people.
- The Committee recognized that oral treatment may be thought of as more convenient for patients; however, the Committee regarded the current price of Gilenya to be too high, given that its effectiveness is about the same as 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, and Dr. Adil Virani.

October 19, 2011 Meeting

Regrets:
Two CDEC members did not attend.

Conflicts of Interest:
None

About this Document:
The information contained within this plain language version of the Canadian Drug Expert Committee (CDEC) Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CDEC:
CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CDEC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CDEC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has requested the deletion of confidential information.