



## CDEC FINAL RECOMMENDATION

### DIMETHYL FUMARATE

(Tecfidera — Biogen Idec Canada Inc.)

**Indication: Relapsing-Remitting Multiple Sclerosis**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that dimethyl fumarate be listed for the treatment of relapsing-remitting multiple sclerosis (RRMS) if both the clinical criterion and the condition are met:

#### **Clinical Criterion:**

- Patients who have a contraindication to, or who have failed to respond to adequate courses of both of the following: at least one interferon beta-1b formulation and glatiramer acetate.

#### **Condition:**

- The patient is under the care of a neurologist who is experienced in the diagnosis and management of multiple sclerosis (MS).

#### **Reasons for the Recommendation:**

1. Two placebo-controlled, randomized controlled trials (RCTs) demonstrated that dimethyl fumarate effectively decreased relapses in RRMS and may be effective in delaying disability progression.
2. The incremental cost effectiveness of dimethyl fumarate is likely to be at least \$65,500 per quality adjusted life year (QALY) compared with glatiramer acetate. The committee felt that there is significant uncertainty with the results of the manufacturer's economic model as CDR identified a number of limitations with the model, such as the manufacturer's indirect comparison, assumptions regarding adverse events, transition probabilities, mortality effect of the Expanded Disability Status Scale (EDSS), and rate of withdrawals from therapy.

#### **Of Note:**

CDEC noted the following:

1. At the submitted price, dimethyl fumarate is not a cost-effective option for initial treatment of RRMS.
2. With regard to the above mentioned recommendation, patients with RRMS previously or currently treated with interferon beta-1a who fail to respond do not require a trial of interferon beta-1b to be eligible for treatment with dimethyl fumarate.

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### **Background:**

Dimethyl fumarate is indicated as monotherapy for the treatment of RRMS to reduce the frequency of clinical exacerbations and to delay the progression of disability. Dimethyl fumarate is currently available as 120 mg delayed-release capsules. The product monograph recommends a starting dose of 120 mg twice daily for seven days, which should be increased to 240 mg twice daily.

### **Summary of CDEC Considerations:**

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

### **Patient Input Information**

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

- People living with MS indicated that the following common symptoms have a major impact on their lives: fatigue; difficulty walking; bladder problems; memory or attention problems; pain, numbness, or tingling; and depression. They noted that MS has a significant impact on their ability to work, creates a financial and emotional burden, and negatively affects their family and social lives.
- Current MS therapies reduce relapses and possibly slow the progression of disability; however, they are limited by the high cost and side effects such as injection site reactions, fatigue, headache, and sore muscles and joints.
- People living with MS indicated that there is a need for additional treatments given the limited effectiveness and toxicities of current therapies, and the challenges associated with subcutaneous or intramuscular injections or infusions. In particular, people living with MS place a great value on oral therapies which could potentially improve their quality of life as well as provide additional treatment choices.

### **Clinical Trials**

Two 96-week RCTs were included in the systematic review (DEFINE and CONFIRM). DEFINE (N = 1237) was a double-blind, three-arm RCT that randomized patients to dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg three times daily, or placebo. CONFIRM (N = 1430) was a four-arm RCT that randomized patients to dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg three times daily, glatiramer acetate 20 mg subcutaneous injection, or placebo. The dimethyl fumarate and placebo groups were double-blind, and the glatiramer acetate group was open-label.

### **Outcomes**

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

- Disability progression — defined as at least a 1.0 point increase on the EDSS from baseline in patients with a baseline score of 1.0 or higher, or at least a 1.5 point increase on the EDSS in patients with a baseline EDSS score of 0, with the increased score sustained 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.

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- Relapse — defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist.
- 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 and the European Quality of Life-5 Dimensions (EQ-5D) questionnaire (visual analog scale and index scores).
- Magnetic resonance imaging (MRI) — used to assess changes in the number and volume of lesions.

The primary outcomes were the proportion of patients with relapse at two years (DEFINE) and the annualized relapse rate at two years (CONFIRM).

### **Results**

Based on the recommended dosing for dimethyl fumarate, CDEC focused its discussion on the results reported for the 240 mg twice daily dosing regimens.

### **Efficacy**

- In DEFINE, fewer dimethyl fumarate patients experienced disability progression versus placebo (16% versus 27%; hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.44 to 0.87), while in CONFIRM, there was no statistically significant difference between dimethyl fumarate and placebo (13% versus 17%; HR 0.79; 95% CI, 0.52 to 1.19) or between glatiramer acetate and placebo (16% versus 17%).
- The proportion of patients who were relapse-free after two years was statistically significantly greater with dimethyl fumarate versus placebo in DEFINE (76% versus 58%,  $P < 0.00001$  by CDR analysis) and in CONFIRM (74% versus 64%,  $P = 0.0003$ ).
- There was a statistically significant improvement in the change from baseline in MSFC for dimethyl fumarate compared with placebo in DEFINE (0.087 versus  $-0.071$ ,  $P = 0.0006$ ) but not in CONFIRM (0.017 versus  $-0.0034$ ,  $P = 0.0576$ ). Glatiramer acetate also failed to demonstrate an improvement in MSFC compared with placebo in CONFIRM (0.049 versus  $-0.0034$ ,  $P = 0.0512$ ).
- In both DEFINE and CONFIRM, EQ-5D visual analog scale scores declined from baseline in both dimethyl fumarate and placebo groups; however, the decline was statistically significantly smaller with dimethyl fumarate compared with placebo in DEFINE ( $-0.28$  versus  $-4.23$ ,  $P = 0.0008$ ). There was no statistically significant difference between dimethyl fumarate and placebo in EQ-5D index scores in either DEFINE or CONFIRM.
- SF-36 physical component scores improved with dimethyl fumarate versus placebo in DEFINE (0.45 versus  $-1.36$ ,  $P = 0.0003$ ) and in CONFIRM (0.49 versus  $-0.71$ ,  $P = 0.0217$ ). There was no statistically significant difference between dimethyl fumarate and placebo for SF-36 mental component scores in either study.

### **Harms (Safety and Tolerability)**

- The proportion of patients who experienced at least one serious adverse event was reported as follows: 18% with dimethyl fumarate and 21% with placebo in DEFINE; 17% with dimethyl fumarate, 22% with placebo, and 16% with glatiramer acetate in CONFIRM. The most common serious adverse events in each study were MS relapses.

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- The proportion of patients who withdrew due to adverse events was reported as follows: 16% with dimethyl fumarate and 13% with placebo in DEFINE; 12% with dimethyl fumarate, 10% with placebo, and 10% with glatiramer acetate in CONFIRM.
- The proportion of patients who experienced at least one adverse event was reported as follows: 96% with dimethyl fumarate and 95% with placebo in DEFINE; 94% with dimethyl fumarate, 92% with placebo, and 87% with glatiramer acetate in CONFIRM. Flushing was the most common adverse event among dimethyl fumarate-treated patients in both studies.

### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost utility analysis comparing dimethyl fumarate with interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), glatiramer acetate, and natalizumab, in patients with RRMS, over a 20-year time horizon. Patients were based on those from the DEFINE and CONFIRM trials. Patients in the economic model were assumed to move between EDSS levels (0 to 10), with higher EDSS scores associated with an increase in mortality and health care costs and with lower quality of life (utility decreases). Patients could also move from RRMS to secondary progressive multiple sclerosis MS. The model also incorporated risks of relapses for each level.

Data on the natural progression in MS were derived primarily from the DEFINE and CONFIRM clinical trial data sets. Data on relative effectiveness of all comparators in terms of disease progression, relapses and withdrawals were obtained through an unpublished network meta-analysis. Utility values were primarily obtained from the DEFINE and CONFIRM clinical trial data sets. Costs for each state were derived from Canadian data. The manufacturer did not distinguish between first- and second-line use of therapies, only compared dimethyl fumarate to one other comparator at a time, and did not consider no treatment in the analysis.

The manufacturer reported that dimethyl fumarate dominates (less costly and more QALYs) Avonex, Rebif 44 mcg, Betaseron and fingolimod and that dimethyl fumarate is associated with an incremental cost per QALY of less than \$46,000 when compared with Rebif 22 mcg, Extavia, glatiramer acetate, and natalizumab.

CDR noted a number of limitations related to the choice of input parameters and assumptions. When CDR attempted to account for the transition probabilities, mortality effect of EDSS, choice of utility values, costs of relapses, rate of withdrawals from therapy, and assumptions around adverse events, the incremental cost per QALY for dimethyl fumarate was approximately \$65,500 when compared with glatiramer acetate and dominated (more QALYs and less costly) Rebif 44 mcg. The reanalyses were unable to address the uncertainty associated with the manufacturer's network meta-analysis.

At the submitted price, the annual cost of dimethyl fumarate is \$██████, which is greater than glatiramer acetate (\$16,241), similar to interferons (\$18,133 to \$24,536), and less than fingolimod (\$31,085) and natalizumab (\$40,171).

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### Other Discussion Points:

The Committee noted the following:

- The long-term safety profile of dimethyl fumarate in the treatment of MS requires further evaluation.
- Orally administered treatments are often considered to be more convenient for patients than those that require intravenous or subcutaneous administration.
- The effect of dimethyl fumarate on MRI outcomes is uncertain given that the MRI cohorts of DEFINE and CONFIRM included less than 50% of all study participants.

### Research Gaps:

The Committee noted that there is an absence of evidence regarding the following:

- There were no studies designed to directly compare dimethyl fumarate against other agents approved for use in the treatment of RRMS.
- There are no long-term outcome data on disability progression from RCTs for dimethyl fumarate or other agents for the treatment of RRMS.

### 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

### Regrets:

**July 17, 2013:** None

**September 18, 2013:** One CDEC member could not attend the meeting.

### 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*.

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