CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

PEGYLATED INTERFERON-BETA 1A
(Plegridy — Biogen Canada Inc.)
Indication: Relapsing-Remitting Multiple Sclerosis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that pegylated interferon (PegIFN) beta-1a be listed for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and slow the progression of disability, if the following clinical criterion and condition are met:

Clinical criterion
- List in a manner similar to other interferon (IFN) products.

Condition
- Drug plan cost for PegIFN beta-1a should not exceed the drug plan cost of any first-line injectable drugs for the treatment of RRMS.

Reasons for the Recommendation:
1. One double-blind, randomized controlled trial (RCT) (ADVANCE; N = 1,516) demonstrated that treatment with PegIFN beta-1a was superior to placebo for reducing the risk of relapse and the progression of disability in patients with mild to moderate RRMS.
2. Two network meta-analyses (NMAs) suggested that PegIFN beta-1a was as effective and safe as other first-line drugs for the treatment of RRMS.
3. At the submitted price, the annual cost of PegIFN beta-1a 125 mcg every two weeks ($21,584) is the same as IFN beta-1a 30 mcg weekly ($21,585), less than IFN beta-1a 44 mcg three times weekly ($24,469), and more than IFN beta-1a 250 mcg every other day ($18,133 to $20,075) and glatiramer acetate 20 mg per day ($16,241). Therefore, a reduction in price is required for PegIFN beta-1a to be cost-neutral compared with other first-line treatment options for RRMS.

Background:
PegIFN beta-1a is indicated for the treatment of RRMS to reduce the frequency of clinical exacerbations and to slow the progression of disability. PegIFN beta-1a is available as a liquid for subcutaneous injection in pre-filled syringes or pens (63 mcg, 94 mcg, or 125 mcg per

0.5 mL). The recommended dose is 63 mcg on day 0, 94 mcg at week 2, and then 125 mcg every two weeks.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of PegIFN beta-1a, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals living with RRMS.

Patient Input Information
One patient group, the Multiple Sclerosis Society of Canada, responded to the CDR call for patient input. Information was obtained from an online survey of MS patients and their caregivers and from publicly available information. The following is a summary of information provided by the patients and caregivers:

- Patients living with MS can experience fatigue, pain, cognitive problems, bladder problems, numbness, weakness, tingling, heat intolerance, problems with balance, dizziness, difficulties in walking, sexual dysfunction, tremor, spasticity, and difficulties in swallowing and/or speaking.
- These symptoms can have a profound negative impact on the quality of life of patients and their caregivers. Physical and cognitive limitations can interfere with employment; education; family commitments; interpersonal relationships; and physical, social, and recreational activities. In addition, treatment regimens can also affect a patient's quality of life through resulting side effects (such as flulike symptoms, injection-site reactions, flushing, and headaches) and difficulties related to administering the drugs.
- Patients reported tremendous variation in disease severity and symptomatology, with no one-size-fits-all therapy. They reported having had experience with a range of both oral and injectable treatments, but noted that some patients would prefer a treatment that required less frequent administration.

Clinical Trials
The CDR systematic review included one randomized, double-blind, parallel-group study. The ADVANCE study (N = 1,516) compared PegIFN beta-1a 125 mcg every two weeks or every four weeks against placebo. ADVANCE was placebo-controlled up to week 48, after which time patients on placebo were randomly allocated to receive either PegIFN beta-1a every two weeks or every four weeks. Blinded treatment continued until week 96. Most patients had mild to moderate disease at baseline (median Expanded Disability Status Scale [EDSS] = 2.5) and the majority of patients were treatment-naive (83%).

Outcomes

- Relapse — new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, with onset more than 30 days after the last relapse, and accompanied by new objective neurological findings observed upon examination by a neurologist.
- Progression of disability — defined as at least a 1.0 point increase on the EDSS from a baseline EDSS ≥ 1.0 sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.

- No Evidence of Disease Activity (NEDA) — defined as the absence of both clinical (no relapses and no onset of 12-week confirmed disability progression over the interval) and magnetic resonance imaging (MRI) (no gadolinium-enhancing lesions and no new or newly enlarging T2 hyperintense lesions) disease activity during the respective time periods. NEDA was included as a post hoc analysis.
- Symbol Digit Modalities Test (SDMT) — a screening test for cognitive impairment involving a simple substitution task. No minimal clinically important difference was identified.
- Health-related quality of life — assessed using the Short Form Health Survey (SF-12), Multiple Sclerosis Impact Scale (MSIS-29), and the EuroQol 5-Dimensions Questionnaire (EQ-5D).

The primary end point was annualized relapse rate at the end of the placebo-controlled phase (week 48).

Efficacy

- In the group receiving PegIFN beta-1a every two weeks, 34% of patients achieved NEDA compared with 15% in the placebo group after 48 weeks (relative risk: 2.2 [95% confidence interval (CI), 1.8 to 2.9]; $P < 0.0001$).
- Ninety (18%) patients in the group receiving PegIFN beta-1a every two weeks and 142 (28%) patients in the placebo group experienced a relapse. The adjusted annualized relapse rate after 48 weeks was 0.256 (95% CI, 0.206 to 0.318) for the PegIFN beta-1a every-two-weeks group and 0.397 (95% CI, 0.328 to 0.481) for the placebo group (rate ratio: 0.644 [95% CI, 0.500 to 0.831]; $P = 0.0007$).
- A statistically significantly lower proportion of patients in the PegIFN beta-1a every-two-weeks group experienced disability progression compared with patients in the placebo group (6% versus 10%; hazard ratio 0.62 [95% CI, 0.40 to 0.97]; $P = 0.04$).
- There were no statistically significant differences between PegIFN beta-1a every two weeks and placebo at week 48 on the MSIS-29, SF-12, EQ-5D index, or the EQ-5D Visual Analogue Scale score. There was also no statistically significant improvement observed in measures of function and cognition (SDMT).
- The MRI results provide evidence for consistency of treatment effect, with comparisons showing less deterioration in the PegIFN beta-1a every-two-weeks group compared with the placebo group at 48 weeks: mean 4.1 versus 13.3 new or newly enlarging T2 hyperintense lesions, respectively, $P < 0.0001$; mean 4.1 versus 13.4 new active lesions, respectively, $P < 0.0001$; mean 0.2 versus 1.4 gadolinium-enhancing lesions, respectively, $P < 0.0001$. The number of patients developing at least one new or newly enlarging T2 hyperintense lesion from baseline to week 48 was lower in the group taking PegIFN beta-1a every two weeks compared with the group taking placebo (59% versus 81%; *P* value not reported).

Harms (Safety and Tolerability)

- A total of 94% of patients in the PegIFN beta-1a every-two-weeks group experienced an adverse event, compared with 83% of patients in the placebo group. The most common adverse events were injection-site reactions and flulike symptoms. Injection-site reactions were reported by 66% of patients who received PegIFN beta-1a every two weeks, compared with 11% of patients receiving placebo.
- The incidence of severe adverse events was numerically higher in the PegIFN beta-1a every-two-weeks group compared with placebo for headache (5% versus 2%), myalgia (2%

versus < 1%), influenza-like illness (5% versus < 1%), pyrexia (3% versus 0%), and injection-site erythema (2% versus 0%).
- In the first year, 11% of patients taking PegIFN beta-1a every two weeks and 15% of patients taking placebo experienced at least one serious adverse event. With the exception of events that were classified as multiple sclerosis relapses, no serious adverse events occurred more than once in the PegIFN beta-1a every-two-weeks group.
- Withdrawals due to adverse events were reported for 5% of patients in the PegIFN beta-1a group and 1% in the placebo group during the first year. The most commonly reported adverse events leading to withdrawal included influenza-like illness, injection-site erythema, and pyrexia.
- Decreases in white blood cell counts of < 3.0 x 10^9/L were reported for 7% of patients receiving PegIFN beta-1a every two weeks and 1% receiving placebo. The incidence of decreases in lymphocyte counts (< 0.8 x 10^9/L) was slightly greater in patients taking PegIFN beta-1a every two weeks (5%), compared with placebo (3%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost analysis comparing the annual drug cost of PegIFN beta-1a (125 mcg every two weeks) with other IFNs (IFN beta-1a 30 mcg weekly, IFN beta-1a 22 mcg or 44 mcg three times weekly, and IFN-beta 1b 250 mcg every other day), and glatiramer acetate (20 mg per day), for the treatment of RRMS. Comparator costs were obtained from Ontario Drug Benefit Exceptional Access Program list prices (April 2015). Clinical efficacy and safety were assumed to be similar between PegIFN beta-1a and comparators on the basis of a published NMA. Health care resource use other than drug usage was assumed to be similar among all comparators.

At the submitted price of $830.15 per dose (regardless of strength), the annual cost of PegIFN beta-1a 125 mcg every two weeks ($21,584 per patient) is identical to that of IFN beta-1a 30 mcg weekly, less than IFN beta-1a 44 mcg three times weekly ($24,469 per patient), and more than other available IFNs for the treatment of RRMS (range from $18,133 to $20,100 per patient) and glatiramer acetate ($16,241 per patient).

CDR conducted pricing scenarios to examine the reduction in price required for PegIFN beta-1a to be cost-neutral to less costly comparators, as well as scenarios incorporating lower list prices available in some jurisdictions for IFN beta-1a 30 mcg weekly. The price reduction required for PegIFN beta-1a varied between 4.6% and 16%, compared with IFNs, and 24.6% compared with glatiramer acetate.

Other Discussion Points:

CDEC noted the following:
- PegIFN beta-1a requires less frequent dosing and is therefore more convenient for patients than some of the other IFNs available for the treatment of RRMS; however, it is unclear whether fewer administrations would be associated with fewer adverse events or greater adherence.
- Patient group and clinical expert input emphasized the need for multiple treatment options for RRMS.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of PegIFN beta-1a against other first-line agents, including glatiramer acetate.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

November 18, 2015 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 not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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