CDEC FINAL RECOMMENDATION

INTERFERON BETA-1A
(Rebif – EMD Serono Canada Inc.)
Indication: Clinically Isolated Syndrome

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that subcutaneous (SC) 44 mcg interferon (IFN) beta-1a not be listed for clinically isolated syndrome (CIS).

Reason for the Recommendation:
One double-bind, randomized controlled trial (RCT) demonstrated that treatment with IFN beta-1a (44 mcg SC three times per week) resulted in a statistically significant delay in the time to conversion from CIS to multiple sclerosis (MS) compared with placebo (hazard ratio [HR] 0.48; 95% CI: 0.31 to 0.73). However, the treatment of CIS with IFN beta-1a has not been shown to affect long-term disability progression; therefore, the clinical benefit is uncertain.

Background:
Rebif (IFN beta-1a) is indicated for the treatment of patients who have experienced a single demyelinating event, accompanied by an active inflammatory process and an abnormal magnetic resonance imaging (MRI) scan, with lesions typical of MS, who are determined to be at high risk of developing clinically definite MS. The Rebif formulation of IFN beta-1a is a purified, sterile glycoprotein product produced by recombinant DNA techniques and is available as a solution for SC injection.

The recommended dose for patients who have experienced a first demyelinating event is 44 mcg three times per week by SC injection. The product monograph recommends administering 20% of the total dose during the initial two weeks of therapy, 50% of the total dose in weeks three and four, and the full dose from the fifth week onwards.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of the Rebif formulation of IFN beta-1a and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR call for patient input.

Clinical Trials

One trial of patients with CIS was included in the systematic review. REFLEX (N = 517) was a 24-month, phase 3, double-blind, placebo-controlled RCT. Patients were randomized to IFN beta-1a 44 mcg SC three times weekly, IFN beta-1a 44 mcg SC once weekly, or placebo. Patients who converted to clinically definite MS during the double-blind phase of REFLEX were switched to open-label treatment with IFN beta-1a SC 44 mcg three times weekly and followed-up for safety events.

Outcomes

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

- Time to conversion to McDonald MS – defined using the 2005 McDonald criteria where a patient was considered to have converted to MS if there was evidence of dissemination in space (DIS) and dissemination in time (DIT) based on clinical data and MRI.
  - DIS was defined by the presence of three of the following four MRI results: gadolinium-enhancing lesions, nine T2 lesions, at least one infratentorial lesion, and at least three periventricular lesions.
  - DIT was defined as the detection of gadolinium-enhancing lesions at least three months after the onset of the initial clinical event, if not at the site corresponding to the initial event; or detection of a new T2 lesion, if appearing at any time, compared with a reference scan done at least 30 days after the onset of the initial clinical event.
- Disability – measured using the Expanded Disability Status Scale (EDSS), an ordinal scale (0 to 10) used to measure disability in MS using eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation.
- Time to conversion to clinically definite MS – defined by either a second clinical event suggestive of MS or a sustained increase (≥ 1.5 points) in the EDSS score for at least three months.
- Relapse – defined as a new or worsening neurological symptom, in the absence of fever, lasting for at least 24 hours, accompanied by an objective change in the relevant functional system, and preceded by at least 30 days of clinical stability or improvement.
- MRI outcomes – assessed changes in the number and volume of lesions.
- Health-related quality of life – measured using the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.

The primary efficacy outcome in REFLEX was time from randomization to MS, as defined by the 2005 McDonald criteria.

Results

CDEC focussed their deliberations on the dosage regimen of IFN beta-1a that is recommended in the product monograph for the treatment of CIS (i.e., 44 mcg three times weekly).

Efficacy

- Compared with placebo, IFN beta-1a demonstrated a statistically significant delay in the time to conversion to clinically definite MS (HR 0.48; 95% CI: 0.31 to 0.73) and McDonald MS (HR 0.49; 95% CI: 0.38 to 0.64).
- The probability of conversion to clinically definite MS was 0.21 and 0.38 for the IFN beta-1a and placebo groups, respectively, and the probability of conversion to McDonald MS was 0.62 in the IFN beta-1a group and 0.76 in the placebo group.

- The mean change in EDSS score from baseline was statistically significantly greater in the IFN beta-1a group compared with placebo (–0.230; 95% CI: –0.417 to –0.044).
- The annualized relapse rate in the IFN beta-1a group was 0.118 compared to 0.220 in the placebo group ($P = 0.001$).
- The cumulative mean number of new gadolinium-enhancing lesions was lower in the IFN beta-1a group compared with placebo (0.8 versus 5.0; $P < 0.001$) and the cumulative mean number of new T2 lesions was lower in the IFN beta-1a group than in the placebo group (2.7 versus 6.7; $P < 0.001$).
- There were no apparent differences between IFN beta-1a and placebo in health-related quality of life, as measured by the EQ-5D.

Harms (Safety and Tolerability)

- A greater proportion of patients in the placebo group reported at least one serious adverse event compared to the IFN beta-1a group (7.0% versus 3.5%). The most frequently reported serious adverse events in the IFN beta-1a group were infections and infestations (1.8%).
- The proportion of patients who reported at least one adverse event was 87% in the IFN beta-1a group and 78% in the placebo group. The most commonly reported adverse events in IFN beta-1a group were influenza-like illness (54%), injection site erythema (29%), and headache (27%).
- Withdrawals due to adverse events were reported for 2.9% of patients in the IFN beta-1a group and 3.5% in the placebo group. The most frequently reported reasons for discontinuation in the IFN beta-1a group were psychiatric disorders (1.2%), and general disorders and administration site conditions (1.2%).

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis comparing 44 mcg SC IFN beta-1a three times weekly to no treatment, in patients with CIS, over a lifetime (50 years) time horizon. The McDonald 2005 criteria were used to define conversion to MS, with scenario analyses performed using Poser criteria. The Markov model was comprised of health states that simulate the spectrum of CIS to MS and their progression through more severe MS states over a lifetime period, and include: CIS on-treatment, CIS off-treatment, relapsing-remitting MS with disease severity by EDSS score, secondary-progressive MS, and death. Within each one-year Markov cycle, patients with CIS either remained with CIS on-treatment, progressed to relapsing-remitting MS (conversion defined either by McDonald criteria or Poser criteria), or discontinued treatment. Patients who discontinued treatment face a higher probability of progressing to MS than those on treatment. Once patients converted to relapsing-remitting MS, within each model cycle they could transition to a lower EDSS score, remain in the current EDSS state, deteriorate to a higher EDSS level, or progress to secondary-progressive MS. In the base case, patients at or above EDSS level 7, or with secondary-progressive MS, were assumed to discontinue treatment.

Treatment effects were modelled as HRs applied to the baseline rate of conversion from CIS to relapsing-remitting MS derived from the placebo arm of REFLEX. Transition probabilities of progressing to MS were taken from the placebo arm of the REFLEX (years 1 and 2) and REFLEXION (year 3) studies. Parametric techniques, which permitted a changing baseline risk of conversion overtime, were used to extrapolate the risk of progression to relapsing-remitting MS beyond three years. The natural history of MS was estimated using the London Ontario MS natural history dataset where patients could not transition to improved EDSS states.

The manufacturer reported that, using the McDonald criteria to define MS, the incremental cost per quality-adjusted life-year (QALY) for IFN beta-1a compared with placebo was $66,139 from the payer perspective. Based on CDR re-analyses, where informal care costs were removed from the payer perspective, the incremental cost-utility ratio (ICUR) for IFN beta-1a was $78,716 (McDonald criteria) or $64,017 (Poser criteria) per QALY. Where uncertainty in the HR of progression from CIS to MS was tested over a plausible range, the ICUR increased to $122,819 (McDonald criteria) and $123,636 (Poser criteria) per QALY. Uncertainty exists in how reducing the risk of progressing from CIS to MS, as demonstrated in short-term studies, translates to clinically important differences in quality of life and survival over time. If model-predicted differences in quality of life and survival accrued over a longer time frame (> 5 years), are attenuated or do not occur, the ICUR will be significantly greater. If the total percentage of patients that convert to MS is 90% (versus 95% in the model using McDonald criteria), the ICUR increases to $117,459 per QALY.

The annual cost for IFN beta-1a 44 mcg SC three times per week is $23,019, which is greater than glatiramer acetate ($16,241), IFN beta-1a 30 mcg intramuscular per week ($20,541), and IFN beta-1b ($18,133 to $20,075).

Other Discussion Points:
CDEC noted that there is no evidence to suggest that IFN beta-1a 44 mcg SC is superior to other less costly products indicated for use in the treatment of CIS.

Research Gaps:
CDEC noted that there were no studies comparing IFN beta-1a 44 mcg SC with other treatment regimens for CIS that are approved for use in Canada.

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.

July 17, 2013 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
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The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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