CDEC FINAL RECOMMENDATION

ELTROMBOPAG OLAMINE
(Revolade – GlaxoSmithKline Inc.)
Indication: Chronic Immune (Idiopathic) Thrombocytopenic Purpura

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that eltrombopag olamine not be listed.

Reasons for the Recommendation:
1. In the three double-blind, randomized placebo-controlled trials of patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP), the primary outcome was platelet response, which the Committee considered less clinically relevant than bleeding events.
2. There are no head-to-head randomized controlled trials (RCTs) comparing eltrombopag with individual comparator treatments for ITP.
3. The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) in excess of *[confidential information removed at manufacturer's request]* for eltrombopag compared with standard of care, for both splenectomized and non-splenectomized patients, which greatly exceeds conventional standards for cost-effectiveness.

Background:
Eltrombopag olamine has a Health Canada indication for adult chronic ITP to increase platelet counts in splenectomized patients who are refractory to first-line treatments (e.g., corticosteroids, immunoglobulins). Health Canada further indicates that eltrombopag olamine may be considered as second-line treatment for adult non-splenectomized patients where surgery is contraindicated.

Eltrombopag olamine is a thrombopoietin receptor agonist. It is available in 25 mg and 50 mg tablets of eltrombopag (as eltrombopag olamine). The Health Canada-recommended starting dose is 50 mg once daily; if after two to three weeks of initial therapy, the platelet counts are below the clinically indicated levels (e.g., 50 x 10^9/L), the dose may be increased to a maximum of 75 mg once daily.

The product monograph indicates that therapy with eltrombopag olamine should not exceed one year of continuous treatment and, that after one year of continuous treatment, therapeutic options should be reassessed.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of eltrombopag olamine and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for patient input. The manufacturer submitted a confidential price for eltrombopag olamine.

Clinical Trials
The systematic review included three double-blind RCTs of adults with a history of primary ITP for greater than three months (the RAISE study) or a minimum of six months (studies 773A and 773B). Patients were required to have previously responded to at least one treatment for ITP and have a baseline platelet count of < $30x10^9$/L. In all trials, randomization was stratified by use or non-use of ITP medications at baseline, splenectomy status, and baseline platelet count (≤ $15x10^9$/L or > $15x10^9$/L). Approximately one-third to one-half of patients enrolled in the three trials were splenectomized, half had baseline platelet counts of ≤ $15x10^9$/L, and approximately half were on an ITP medication at baseline.

- Study 773A (N = 118, 6-week duration) randomized patients to one of three fixed doses of eltrombopag (30 mg, 50 mg, or 75 mg; all once-daily) or placebo. No dosage adjustments were allowed; however, patients achieving platelet counts of > $200x10^9$/L were to discontinue study treatment. Study 773A was stopped early based on an interim analysis that showed the predetermined efficacy stopping criteria were met for eltrombopag 50 mg and 75 mg.
- Study 773B (N = 114, 6-week duration) randomized patients to eltrombopag 50 mg daily or placebo. The dose of eltrombopag could be increased to 75 mg daily based on platelet response on or after day 22. Patients achieving platelet counts of > $200x10^9$/L were to discontinue study treatment.
- RAISE (N = 197, 6-month duration) randomized patients to eltrombopag 50 mg daily or placebo. The dose of eltrombopag could be adjusted between 25 mg to 75 mg daily, based on platelet response.

Patients in all three trials were allowed to receive concomitant ITP medications, provided the dose of the medications was stable at baseline. In RAISE, patients could taper or discontinue baseline ITP medications based on platelet response, and use rescue therapy (defined as a composite of new ITP medication, increased dose of concomitant ITP medication, platelet transfusion, or splenectomy); patients requiring rescue were considered non-responders for the duration of rescue treatment and until platelet counts fell to < $50x10^9$/L after stopping rescue treatment.

In RAISE, 15% of patients withdrew during the 6-month treatment period; the frequency of withdrawal did not differ substantially between eltrombopag and placebo treatment groups. In studies 773A and 773B a high proportion of patients did not complete six weeks of treatment; 43% and 32% of patients randomized to eltrombopag 50 mg, compared with 24% and 21% in the respective placebo groups. The majority of eltrombopag-treated patients who did not

complete the six weeks of treatment in studies 773A and 773B discontinued due to achievement of platelet response.

No RCTs comparing eltrombopag with individual comparator treatments for ITP were identified.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: platelet response, bleeding events, quality of life, need for rescue treatments, and adverse events.

The primary outcome in all trials was the proportion of patients with platelet response, defined as a platelet count of ≥ $50x10^9$/L after up to 42 days of treatment in studies 773A and 773B, and defined as a platelet count between $50x10^9$/L and $400x10^9$/L during six months of treatment in the RAISE trial.

Clinically significant bleeding events were defined as those classified as World Health Organization grades 2 to 4. In all trials, quality of life was assessed using the SF-36, Version 2.

Results

Efficacy or Effectiveness

Given the limited duration of studies 773A and 773B the Committee focused its discussion on the RAISE trial. The efficacy results reported below are specific to the RAISE trial unless otherwise indicated.

- The percentage of patients achieving the primary outcome (platelet response) was statistically significantly higher for eltrombopag 50 mg compared with placebo; 52% versus 17%, respectively, at 26 weeks. Further, eltrombopag increased platelet counts irrespective of the use of baseline ITP medications, splenectomy status, or baseline platelet counts.
- The percentage of patients experiencing a clinically significant bleeding event at end of treatment was not statistically significantly different between eltrombopag and placebo; 10% versus 13% respectively.
- The percentage of patients with any bleeding event from baseline to end of treatment was statistically significantly lower in the eltrombopag group compared with placebo. However, the difference between eltrombopag and placebo-treated patients was no longer statistically significant two weeks after treatment discontinuation.
- The percentage of patients receiving rescue during the treatment period was statistically significantly lower in the eltrombopag group compared with placebo (18% versus 40%), and a statistically significantly greater percentage of eltrombopag-treated patients receiving ITP medications at baseline discontinued one or more baseline ITP medications compared with placebo (47% versus 32%).
- Statistically and clinically important differences in several of the domains of the SF-36, Version 2, were observed favouring eltrombopag, including physical role, vitality, and emotional role.
- In studies 773A and 773B the percentage of patients achieving the primary outcome (platelet response) at six weeks was statistically significantly higher for eltrombopag 50 mg compared with placebo (70% versus 11% and 59% versus 16%, respectively); however, the

frequency of clinically significant bleeding events was not reported. Further, no differences in quality of life, as measured by the SF-36, Version 2, were observed between eltrombopag and placebo in studies 773A and 773B.

Harms (Safety and Tolerability)

- The frequency of withdrawal due to adverse events was similar between eltrombopag and placebo treatment groups in all three trials; range 4% to 9% versus 5% to 10%, respectively.
- The percentage of patients experiencing serious adverse events was similar between eltrombopag and placebo in all three trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis of eltrombopag compared with alternate management strategies for the treatment of adult patients with ITP who are refractory to first-line therapy. Two distinct populations were modelled: those who have undergone splenectomy, and those in whom splenectomy is contraindicated. Eltrombopag was compared to standard of care (which may include corticosteroids, immunosuppressive agents, and rescue therapy) and intravenous immunoglobulin (IVIg). In secondary analyses, other comparators such as Anti-D and rituximab were considered. Clinical data was obtained from the RAISE trial (for eltrombopag and standard of care), and from other clinical studies (for comparators) used in a naive indirect comparison. *[The manufacturer requested that results of the economic analysis remain confidential; three sentences have been removed from this document.]*

CDR noted a number of limitations with the manufacturer's analysis. Clinical effectiveness estimates for eltrombopag versus comparators (other than standard of care) were based on data from non-controlled, non-randomized studies and naive indirect comparisons, and used a surrogate outcome of platelet count rather than focusing on complications of ITP (e.g., bleeds). The manufacturer considered quality of life implications for both the complications associated with ITP (e.g., bleeds), as well as implications for reduced platelet counts. It is unclear whether quality of life improvements would occur based on improved platelet counts alone (no change in bleeds), which may overestimate the clinical benefit associated with eltrombopag compared with standard care. While the manufacturer considered a number of comparators, the most appropriate comparator is likely standard of care, as other treatments tend to be used as temporary solutions or as a bridge to splenectomy, rather than long-term treatment.

At recommended doses, the drug acquisition cost of eltrombopag (*[confidential price removed at manufacturer's request]* annually) is greater than standard of care (e.g., prednisone $65 to $75 annually) and Anti-D ($1,350 to $2,700 per administration) if used on a regular basis (i.e., every four weeks). The cost of IVIg is $4,808 to $9,615 per administration.

Patient Input Information:

No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:

- The Committee was unable to identify a subpopulation of patients for whom treatment with eltrombopag may be beneficial.
- The Committee considered that the identification and classification of bleeding events in the trials may have been biased due to investigators' knowledge of platelet counts.

- The Committee discussed that there is limited long-term safety evidence for eltrombopag, particularly related to the risk of hematological complications and cataract formation. The Committee noted the short duration of trials and the Health Canada recommendation that eltrombopag therapy should not exceed one year of continuous treatment, after which therapeutic options should be reassessed. The Committee noted the possibility that patients may be restarted on eltrombopag when signs and symptoms of ITP recur.

CDEC Members:
Dr. Robert Peterson (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. Lindsay Nicolle, Dr. Yvonne Shevchuk, Dr. James Silvius, Dr. Adil Virani.

September 21, 2011 Meeting

Regrets:
One CDEC member 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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