Canadian Drug Expert Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Revolade, which is also called eltrombopag olamine, not be listed by Canada's publicly funded drug plans for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP).

Reasons for the Recommendation:
1. In the three medical studies reviewed by CDEC of patients with chronic ITP, the main purpose was to measure blood platelet counts. The Committee considered blood platelet counts to be less important to patients than the number of bleeding events.
2. There are no good-quality studies comparing Revolade with the various other treatments available for ITP.
3. Results of the manufacturer's economic analysis suggested that Revolade is not cost-effective compared with standard of care, either for patients who had their spleen removed (splenectomized) or those who had not (non-splenectomized). *[Confidential cost-effectiveness estimate removed at manufacturer's request.]*

Background:
ITP is a condition in which there is a low platelet count. Platelets are blood cells that help the blood to clot. ITP patients may have an increased risk of bleeding. Symptoms of bleeding are petechiae (pinpoint-sized, flat, round red spots under the skin), purpura (bruising), nosebleeds, bleeding gums, or not being able to control bleeding if cuts or injuries occur.

Revolade is a thrombopoietin receptor agonist. It works by causing new platelets to be formed.

Revolade has a Health Canada indication for adult chronic ITP to increase platelet counts in splenectomized patients who are refractory to (not improving with) first-line treatments (e.g., corticosteroids, immunoglobulins). Health Canada further indicates that Revolade may be considered as a second-line treatment for adult non-splenectomized patients where surgery is contraindicated (not appropriate).

Revolade is available as 25 mg and 50 mg tablets. The Health Canada recommended starting dose is 50 mg once daily; if, after two to three weeks of treatment, the platelet counts continue

to be lower than the level that is good for the patient (e.g., 50 x 10^9/L), the dose may be increased to a maximum of 75 mg once daily. The product monograph states that treatment with Revolade should not be longer than one year (i.e., one year of ongoing treatment) and that after one year of treatment, options should be reassessed.

Summary of CDEC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Revolade and a review of economic information prepared by the manufacturer of Revolade. No patient groups responded to the CDR Call for Patient Input. The manufacturer submitted a confidential price for Revolade.

Clinical Trials
The Committee reviewed three studies of adults with primary (not due to another disease) ITP for more than three months (the RAISE study) or for at least six months (studies 773A and 773B). To be included in the studies, patients had to have shown improvement from at least one previous treatment for ITP and have a platelet count of ≤ 30x10^9/L at study start. In all studies, patients were divided into treatment groups based on use or non-use of ITP medications at study start, splenectomy status (splenectomized versus non-splenectomized), and platelet count (≤ 15x10^9/L versus > 15x10^9/L) so that approximately equal numbers of each type of patients were in each treatment group. Approximately one-third to one-half of patients in the three studies were splenectomized, half had platelet counts of ≤ 15x10^9 at study start, and approximately half were on an ITP medication at study start.

- Study 773A included 118 patients. Patients were given one of three doses of Revolade (30 mg, 50 mg, or 75 mg) or placebo (a tablet containing no active medication) once daily for six weeks. The dosage of the medication could not be changed during the study. However, patients who reached platelet counts of > 200x10^9/L had to stop the study treatment. Study 773A was stopped early because an interim analysis (analysis of data before the planned end of study) showed that Revolade 50 mg and 75 mg were better than placebo.
- Study 773B included 114 patients. Patients were given either Revolade 50 mg or placebo, daily for six weeks. The dose of Revolade could be increased to 75 mg daily based on platelet count on or after day 22. Patients reaching platelet counts of > 200x10^9/L had to stop the study treatment.
- The RAISE study included 197 patients. Patients were given either Revolade 50 mg or placebo, daily for six months. The dose of Revolade could be adjusted to between 25 mg and 75 mg daily, based on the platelet count.

Patients in all three studies were allowed to receive other ITP medications, if the dose of these medications had been stable prior to study start. In RAISE, patients could decrease or stop these ITP medications based on platelet counts. Patients were also allowed to receive “rescue” therapy (defined as one or more of a new ITP medication, increased dose of ongoing ITP medication, platelet transfusion, or splenectomy). Patients who needed rescue therapy were considered to be non-responders for the period of rescue treatment and until platelet counts fell to < 50x10^9/L after stopping rescue treatment.

In RAISE, 15% of patients stopped participating during the six-month treatment period; this was about the same for Revolade and placebo treatment groups. In studies 773A and 773B, a high

proportion of patients did not finish the six weeks of treatment: 43% and 32% of patients given Revolade 50 mg, compared with 24% and 21% in the respective placebo groups. The majority of Revolade-treated patients who did not finish the six weeks of treatment in studies 773A and 773B stopped taking part in the study because their platelet counts had improved and were at a good level.

No studies comparing Revolade with other treatments for ITP were found.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: platelet response, bleeding events, quality of life, need for rescue treatment, and side effects.

The main purpose in all of the studies was to measure the percentage 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 study.

Clinically significant bleeding events were defined as those classified as World Health Organization grades 2 to 4. Quality of life was assessed using the 36-item Short Form Health Survey (SF-36) version 2 in all of the studies.

Results

Efficacy or Effectiveness

As studies 773A and 773B were short, the Committee focused its discussion on the RAISE study. The results reported below are specific to the RAISE study, unless otherwise stated:

- The percentage of patients who had a platelet response was greater for Revolade 50 mg than placebo: 52% versus 17%, respectively, at 26 weeks. Further, Revolade increased platelet counts regardless of whether patients were on ITP medications at study start or were splenectomized, and regardless of their platelet count at study start.
- The percentage of patients who had a clinically significant bleeding event by the end of the treatment was about the same for Revolade and placebo: 10% versus 13%, respectively.
- The percentage of patients with any bleeding event from study start to end of treatment was lower in the Revolade group than in the placebo group. However, at two weeks after the treatment was stopped, there was no real difference between the Revolade- and placebo-treated patients.
- The percentage of patients who had rescue treatment during the treatment period was lower in the Revolade group than in the placebo group (18% versus 40%), and a higher percentage of Revolade-treated patients receiving ITP medications at the beginning of the study stopped one or more of these medications than placebo patients (47% versus 32%).
- Patients on Revolade, compared with placebo, showed more improvement on several sections of the SF-36 version 2 questionnaire, including physical role, vitality (energy), and emotional role.
- In studies 773A and 773B, the percentage of patients who had a platelet response at six weeks was higher for Revolade 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 seen between Revolade and placebo in studies 773A and 773B.

Harms (Safety and Tolerability)

- The percentage of patients stopping participation in the study due to side effects was similar regardless of whether they were on Revolade or placebo treatment in all three studies (range 4% to 9%, versus 5% to 10%, respectively).
- A similar percentage of patients had a serious side effect with Revolade as with placebo in all three studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Revolade with other options for the treatment of adult patients with ITP who are refractory to first-line therapy, to evaluate the health benefit. The manufacturer looked at two groups of patients: those who have undergone splenectomy and those in whom splenectomy is not appropriate. Revolade was compared with standard of care (which may include corticosteroids, immunosuppressive agents, and rescue therapy) and intravenous immunoglobulin. In further analyses, Revolade was compared with other medications, including Anti-D and rituximab. Data were taken from the RAISE study (for Revolade and standard of care) and from other medical studies (for other medications) to estimate how these different treatments compared with each other. *[Confidential results of the economic analysis were removed at manufacturer's request.]*

CDR noted a number of potential problems with the manufacturer's analysis. Effectiveness estimates for Revolade versus comparators (except for standard of care) were based on low-quality studies and looked at platelet count rather than focusing on complications of ITP (e.g., bleeds). The manufacturer considered the potential effects on quality of life of both bleeds and 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 benefit of Revolade compared with standard of 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 cost of Revolade *([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 group of patients for whom treatment with Revolade may be helpful.
- The doctors overseeing the patients in the studies knew the platelet counts of the patients, and the Committee considered that this could have had an effect on the detection of

bleeding events in the studies, as well as on the assessment of the severity of the bleeding events.

- The Committee discussed that there is limited long-term safety evidence for Revolade, particularly related to the risk of blood complications and cataracts (cloudiness of the lens of the eye). The Committee pointed out the short length of the studies and the Health Canada recommendation that Revolade therapy not be longer than one year of ongoing treatment, after which treatment should be reassessed. The Committee noted the possibility that patients may be restarted on Revolade when signs and symptoms of ITP return.

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
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.