



CDEC FINAL RECOMMENDATION

ELTROMBOPAG OLAMINE (Revolade — GlaxoSmithKline Inc.)

Indication: Thrombocytopenia Associated With Chronic Hepatitis C Infection

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that eltrombopag be listed for the treatment of thrombocytopenia in patients with genotype 2 or 3 chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon (IFN)-based therapy, if the following clinical criteria and condition are met:

Clinical Criteria:

- Patient is under the care of a physician treating HCV in a specialized center.
- Patient does not have access to an IFN-free regimen for HCV, and their clinical condition does not permit deferral of treatment until an IFN-free regimen becomes accessible.

Condition:

- Substantial reduction in price.

Reason for the Recommendation:

1. Three double-blind placebo-controlled trials demonstrated that treatment with eltrombopag facilitated the initiation of IFN and ribavirin (RBV) antiviral therapy (AVT) by increasing platelet counts to a required threshold. A statistically significantly greater proportion of eltrombopag-treated patients achieved sustained virologic response (SVR) compared with placebo in the ENABLE-1 and ENABLE-2 randomized controlled trials (RCTs).
2. Eltrombopag is associated with important adverse effects, including thromboembolic events, hepatobiliary adverse events, and events suggestive of hepatic decompensation. Exposure to these risks needs to be weighed carefully by treating clinicians in the context of emerging IFN-free approaches to the treatment of HCV.
3. Based on the CADTH Common Drug Review's (CDR) estimated incremental cost-utility ratio (ICUR) of \$90,060 per quality-adjusted life-year (QALY) for eltrombopag-enabled IFN treatment versus treatment with a reduced dose of IFN or no IFN treatment, CDEC concluded that eltrombopag is not a cost-effective treatment option for patients with genotype 2 or 3 chronic HCV at the submitted price (\$62.50 per 25 mg and \$125.00 per 50 mg tablet).

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Of Note:

- CDEC recognizes that the role of IFN in the treatment of HCV is diminishing, given the increasing availability of IFN-free regimens; therefore, the longer-term clinical relevance of a treatment such as eltrombopag to support IFN plus RBV therapy is uncertain.
- The use of eltrombopag in the ENABLE-1 and ENABLE-2 clinical trials is unlikely to be reflective of routine clinical practice in Canada.

Background:

Eltrombopag is indicated to increase platelet counts in thrombocytopenic patients with chronic HCV infection to allow for the initiation and maintenance of IFN-based therapy. It is also indicated for treatment of adults with chronic immune thrombocytopenia purpura. Eltrombopag is available as 25 mg and 50 mg tablets. The product monograph recommends that eltrombopag be initiated at a dose of 25 mg once daily. The dose should be adjusted in 25 mg increments every two weeks, to a maximum of 100 mg once daily, as required to achieve the target platelet count required to initiate AVT.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs of eltrombopag, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals with thrombocytopenia associated with chronic HCV infection.

Patient Input Information

The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- Patients with HCV may suffer from low platelets due to cirrhosis and are at risk of mortality from bleeding, particularly from bleeding varices. Thrombocytopenia makes it difficult and sometimes impossible for affected patients to receive treatment for their hepatitis C, which may increase their risk of developing severe liver damage, such as cirrhosis.
- Patients reported that those with chronic HCV and low platelets are currently given infusions, injections, and — less frequently — transfusions, which are both painful and inconvenient.
- Patients indicated that they would be willing to tolerate fairly severe side effects if it meant they could be cured.

Clinical Trials

The CDR systematic review included three double-blind, placebo-controlled RCTs (ENABLE-1, ENABLE-2, and TPL102357). ENABLE-1 (N = 682) and ENABLE-2 (N = 759) were phase 3 trials designed to assess the efficacy and safety of eltrombopag as supportive therapy to increase platelets to sufficient levels to facilitate the initiation and maintenance of IFN plus RBV therapy in patients with thrombocytopenia associated with chronic HCV infection. The trials were identically designed, with the exception of the type of IFN used and the corresponding platelet threshold for initiating AVT. ENABLE-1 used peginterferon alfa-2a (Pegasys), which requires a platelet threshold of ≥ 90 Gi/L for initiating AVT, and ENABLE-2 used peginterferon alfa-2b (PEG-Intron), which requires a platelet threshold of ≥ 100 Gi/L for initiation. Both ENABLE-1 and ENABLE-2 consisted of two parts: Part 1 was an initiation pre-AVT phase and Part 2 was a randomized, double-blind, placebo-controlled AVT phase. During Part 1, patients received eltrombopag in a dose-escalating fashion (i.e., eltrombopag 25 mg to 100 mg once

daily for two to nine weeks) depending upon platelet response. Patients who achieved the minimum platelet threshold for initiating AVT were randomized 2:1 to eltrombopag or placebo in Part 2, where they were treated for 24 to 48 weeks (genotype 2 or 3) or 48 weeks (genotype other than 2 or 3).

Study TPL102357 was a phase 2, multi-centre RCT that assessed whether eltrombopag could increase platelet counts in patients with thrombocytopenia associated with cirrhosis due to chronic HCV infection. Participants were randomized 1:1:1:1 to eltrombopag 30 mg once daily, 50 mg once daily, 75 mg once daily, or placebo. In the initial treatment phase (Part 1), patients received eltrombopag or placebo according to their randomized treatment for four weeks. Patients who completed the initial phase were eligible for AVT if they achieved the minimal platelet threshold count of > 70 Gi/L for peginterferon alfa-2a or > 100 Gi/L for peginterferon alfa-2b (chosen at the investigator's discretion). In the AVT phase (Part 2), patients received peginterferon plus RBV for eight to 16 weeks.

Outcomes

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

- SVR — defined as the proportion of study participants with undetectable serum HCV RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment.
- Rapid virologic response (RVR) — defined as undetectable HCV RNA after four weeks of AVT.
- Early virologic response (EVR) — defined as a clinically significant reduction in HCV RNA (> 2 log₁₀ drop or undetectable) after 12 weeks of AVT.
- End of treatment response (ETR) — defined as undetectable HCV RNA at the end of AVT.
- SVR at 12 weeks (SVR12) — defined as undetectable HCV RNA at the end of AVT and at the 12-week follow-up.
- Complete EVR (cEVR) — defined as undetectable HCV RNA at 12 weeks.
- Platelet counts
- Short-Form 36-Item Health Survey (SF-36) — a generic, 36-item, nine-question, patient self-report survey of health status and health-related quality of life. It produces an eight-scale profile (i.e., physical function, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social function, role limitations due to emotional problems, and mental health) and two summary indexes (component scores) for physical and mental health.
- Chronic Liver Disease Questionnaire-Hepatitis C Virus (CLDQ-HCV) — a 29-item patient self-report questionnaire developed for measurement of health-related quality of life among patients with chronic liver disease and HCV. The CLDQ-HCV assesses four domains: activity/energy, emotion, systemic symptoms, and worry. A higher score indicates better quality of life. A clinically important difference is defined as a change in score of 0.5.
- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms.

The primary end points of the included studies were the rate of SVR (ENABLE-1 and ENABLE-2) and the proportion of patients with a shift from baseline platelet count (between 20 Gi/L and ≤ 70 Gi/L) to ≥ 100 Gi/L after four weeks (TPL102357).

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Efficacy

- A statistically significantly greater proportion of eltrombopag-treated patients achieved SVR compared with placebo in both ENABLE-1 (23% versus 14%; $P = 0.0064$) and ENABLE-2 (19% versus 13%; $P = 0.0202$). The percentage difference between the eltrombopag and placebo groups was 7.9% (95% confidence interval [CI], 2.4 to 13.4) in ENABLE-1 and 6.0% (95% CI, 1.2 to 10.9) in ENABLE-2.
- Subgroup analyses demonstrated that the proportion of patients who achieved SVR was numerically greater with eltrombopag than with placebo for those with genotype 2 or 3 (eltrombopag versus placebo: 35% versus 24% in ENABLE-1 and 18% versus 10% in ENABLE-2) and for those with non-genotype 2 or 3 (eltrombopag versus placebo: 18% versus 10% in ENABLE-1 and 13% versus 7% in ENABLE-2). The percentage difference between the eltrombopag and placebo groups was reported as follows:
 - Genotype 2 or 3: 9.2% (95% CI, -3.0 to 21.5) in ENABLE-1 and 10.4% (95% CI, -2.4 to 23.3) in ENABLE-2
 - Non-genotype 2 or 3: 7.6% (95% CI, 1.4 to 13.7) in ENABLE and 5.3% (95% CI, 0.1 to 10.6) in ENABLE-2.
- There were no statistically significant differences between eltrombopag and placebo in the proportion of patients who achieved RVR or extended rapid virologic response (eRVR). There was a statistically significant difference in the proportions of patients who achieved EVR, cEVR, ETR, and SVR12. The percentage difference between the eltrombopag and placebo groups was reported as follows (ENABLE-1 and ENABLE-2, respectively):
 - RVR: 1.0% (95% CI, -2.5 to 4.5) and 1.6% (95% CI, -1.8 to 5.1)
 - eRVR: 16.7% (95% CI, 9.2 to 24.1) and 20.7% (95% CI, 13.6 to 27.8)
 - cEVR: 14.8% (95% CI, 8.6 to 21.1) and 9.1% (95% CI, 3.5 to 14.7)
 - ETR: 10.7% (95% CI, 3.3 to 18.1) and 13.1% (95% CI, 6.9 to 19.4)
 - SVR12: 8.3% (95% CI, 2.7 to 13.9) and 8.6% (95% CI, 3.7 to 13.5).
- In the ENABLE trials, there were no statistically significant differences between the eltrombopag and placebo groups in the change from baseline in SF-36 scores. The only statistically significant difference in the change from baseline in CLDQ-HCV was in the Worry subscale in ENABLE-2 (treatment difference 2.6 [95% CI, 1.1 to 4.1]; $P = 0.001$).
- More patients had minimum platelet counts < 50 Gi/L in the placebo groups of ENABLE-1 (85%) and ENABLE-2 (76%) compared with patients treated with eltrombopag (32% and 19%, respectively). In ENABLE-1 and ENABLE-2, the eltrombopag groups demonstrated greater maximum continuous durations of platelet counts ≥ 50 Gi/L (25.6 and 26.3 weeks) compared with the placebo groups (7.5 and 9.7 weeks, respectively).

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was:
 - ENABLE-1: 20% with eltrombopag and 15% with placebo
 - ENABLE-2: 20% with eltrombopag and 15% with placebo
 - TPL102357: 11% with eltrombopag and 6% with placebo.
- The proportion of patients with at least one adverse event was:
 - ENABLE-1: 96% with eltrombopag and 97% with placebo
 - ENABLE-2: 94% with eltrombopag and 93% with placebo
 - TPL102357: 70% with eltrombopag and 17% with placebo.
- The proportion of patients who withdrew from the trial due to adverse events was:
 - ENABLE-1: 19% with eltrombopag and 29% with placebo

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- ENABLE-2: 23% with eltrombopag and 28% with placebo
- TPL102357: 9% with eltrombopag and 0% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis over a lifetime horizon of 50 years, conducted from a Canadian public payer perspective, in adults with HCV who had a platelet count precluding AVT. The primary comparison was between eltrombopag enabling treatment and subsequent maintenance treatment alongside AVT (Peg-IFN–based regimen) versus no enabling treatment and a reduced dose of Peg-IFN (when platelets are in 25,000/ μ L to 90,000/ μ L ranges) and no Peg-IFN treatment for patients with platelets less than 25,000/ μ L. The manufacturer reported that eltrombopag enabling and maintenance treatment alongside full-dose AVT compared with no enabling treatment, followed by reduced-dose AVT, results in an incremental cost per QALY of \$106,926, or \$55,446 per QALY when considering only patients who are genotype 2 or 3.

CDR noted the following key limitations with the manufacturer's pharmacoeconomic submission:

- In the economic model, patients were required to have platelet levels of 90,000/ μ L to 100,000/ μ L in order to start antiviral therapy, reflecting the ENABLE-1 and ENABLE-2 trials. Although these thresholds are in line with the Canadian product monographs for peginterferon-alfa-2a and -2b, they may not accurately represent current Canadian clinical practice of more aggressive treatment and initiating AVT in much lower platelet counts. This assumption could not be assessed by CDR and may bias efficacy results in favour of eltrombopag.
- For the comparator (reduced-dose AVT regimen), the manufacturer assumed larger dose reductions than have been recommended and used in clinical practice, which bias the results in favour of eltrombopag.
- The manufacturer modelled reduced-dose AVT, based on an unpublished burden of illness study conducted in Quebec, in which "reduced-dose" treatment refers to a reduced duration of treatment, rather than a reduced dose, which is not appropriate.
- The long-term HCV costs were based on a study conducted in 2005; however, a more recently published Canadian longitudinal cohort study examining the costs associated with HCV (2010) is available.
- The main data source for the natural progression of the disease was the HALT-C study, supplemented with published literature. Alternative published information on the natural history of the disease was considered by CDR.
- The economic analysis was based on a 50-year time horizon. Considering that the average baseline age of trial patients is 51 years, CDR considered a 30-year time horizon to be more appropriate.
- The manufacturer assumed that patients with HCV genotype 2 or 3 were treated for 24 weeks and patients with other genotypes were treated for 48 weeks. As per the Canadian guidelines, previously untreated patients with genotype 2 or 3 would generally receive 24 weeks of AVT; however, if they do not have an RVR at four weeks, and have other predictors of poor response, they may benefit from 36 to 48 weeks of AVT. Longer AVT treatment duration will lead to higher ICURs.

When addressing the identified limitations, CDR estimated the ICUR of enabling and maintenance treatment with eltrombopag compared with reduced-dose of AVT for the treatment of thrombocytopenia to be \$166,040 per QALY for all patients and \$90,060 for patients who are

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genotype 2 or 3. Based on the revised estimate, a 50% price reduction would be required for the incremental cost per QALY to fall below \$50,000 for patients who are genotype 2 and 3, or less than \$100,000 for all patients.

The submitted price for eltrombopag is \$62.50 and \$125 for 25 mg and 50 mg tablets, respectively. At the recommended dose of 25 mg to 100 mg daily, the daily cost of eltrombopag ranges from \$62.50 to \$250.00.

Other Discussion Points:

CDEC noted that routine clinical practice in Canada involves the use of IFN-based therapies at lower platelet thresholds than those used in the ENABLE-1 and ENABLE-2 clinical trials.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the long-term safety profile of eltrombopag to increase platelet counts in thrombocytopenic patients with chronic HCV and this requires further evaluation.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

February 18, 2015 Meeting

Regrets:

Two CDEC members were unable to 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 not requested the removal of confidential information.

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