



CDEC FINAL RECOMMENDATION

BOCEPREVIR

(Victrelis – Merck Canada Inc.)

Indication: Hepatitis C, Chronic

This recommendation supersedes the Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated October 24, 2011.

Recommendation:

CDEC recommends that boceprevir be listed for the treatment of chronic hepatitis C genotype 1 infection in patients with compensated liver disease, in combination with peginterferon alpha (PegIFN α)/ribavirin (RBV), if all of the following clinical criteria and conditions are met:

Clinical Criteria:

- detectable levels of hepatitis C virus (HCV) RNA in the last six months
- a fibrosis stage of F2, F3, or F4.

Conditions:

- a reduced price
- one course of treatment only (up to 44 weeks duration).

Reasons for the Recommendation:

1. In three double-blind, randomized controlled trials (RCTs) comparing placebo with boceprevir, both in combination with PegIFN α /RBV, a statistically significantly higher percentage of boceprevir-treated patients achieved a sustained virologic response (SVR); the benefit of boceprevir was observed both in treatment-naïve patients, and in patients who had either not had an adequate response or had relapsed after previous PegIFN α /RBV therapy.
2. At the submitted price, boceprevir costs between \$25,200 to \$46,200 for one 24 to 44-week course of therapy not including the cost of PegIFN α /RBV or erythropoietin. There was considerable uncertainty around cost-effectiveness estimates for boceprevir. When conservative model inputs were considered, cost per quality-adjusted life-year (QALY) values for boceprevir increased in excess of \$100,000 per QALY, particularly in patients with a low degree of liver fibrosis.

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Of Note:

1. CDEC considered response-guided therapy to be more cost-effective than a full course of therapy (44 weeks of boceprevir) in patients for whom response-guided therapy is appropriate.
2. CDEC noted that the product monograph recommends discontinuation of therapy in all patients with:
 - HCV RNA levels \geq 100 IU/mL at treatment week 12, or
 - Confirmed detectable HCV RNA levels at treatment week 24.
3. There are no RCTs which examine the clinical benefit of repeated courses of boceprevir in patients with chronic hepatitis C infection.
4. Patients co-infected with HIV and HCV were excluded from the RCTs that were included in the 2011 Common Drug Review (CDR) assessment of boceprevir. CDEC noted that the use of boceprevir in patients co-infected with HIV and HCV continues to be investigated and that boceprevir may provide clinical benefit in this patient population, where there is an unmet therapeutic need. The treatment of patients co-infected with HIV and HCV should be under the direction of a physician experienced in managing such patients.
5. In both SPRINT-2 and RESPOND-2 trials, liver fibrosis staging was performed using liver biopsy. CDEC noted that, while liver biopsy is the reference standard for fibrosis staging, non-invasive diagnostic testing is increasingly being used as an alternative in clinical practice.

Background:

Boceprevir has a Health Canada indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with PegIFN α /RBV in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy. Boceprevir, a protease inhibitor, is available as 200 mg capsules and the recommended dose is 800 mg three times daily. The product monograph states that boceprevir should be used in combination with PegIFN α /RBV and should not be used as monotherapy. The product monograph also states that the safety and efficacy of boceprevir alone or in combination with PegIFN α /RBV for the treatment of chronic hepatitis C genotype 1 infection have not been established in patients co-infected with HIV and HCV.

Submission History:

In September 2011, CDEC issued a recommendation that boceprevir be listed for the treatment of chronic hepatitis C genotype 1 infection in patients with compensated liver disease, in combination with PegIFN α /RBV. The CDR participating drug plans requested clarification on two of the clinical criteria in the original CDEC recommendation:

- “a fibrosis stage, based on liver biopsy, of F2, F3, or F4” – CDEC was asked to clarify if liver biopsy is the only acceptable method for fibrosis staging or if other methods could also be acceptable.
- “patients not co-infected with HIV” – Given the emerging evidence for the use of boceprevir in patients co-infected with HIV and HCV, CDEC was asked to clarify if there is a role for boceprevir in this patient population.

Summary of CDEC Considerations:

CDEC considered the following information in the 2011 review of boceprevir:

- a systematic review of double-blind RCTs

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- a critique of the manufacturer's pharmacoeconomic evaluation
- patient group-submitted information.

CDEC considered the following information to address the request for advice:

- Materials included in the CDEC brief for the 2011 review of boceprevir
- The original CDEC recommendation for boceprevir (October 24, 2011)
- The CDR *Request for Advice Brief*, which included the following:
 - an updated literature search from a previous Canadian Agency for Drugs and Technologies in Health (CADTH) *Rapid Response* report on non-invasive methods for fibrosis staging in patients with chronic hepatitis C infection (*Diagnosis and Monitoring of Liver Fibrosis in Patients with Chronic Hepatitis C: A Review of the Clinical Evidence and Cost-Effectiveness*)
 - an updated literature search from a CADTH *Rapid Response* report assessing the use of NS3 protease inhibitors in HCV/HIV co-infected patients (*Protease Inhibitor Use for Chronic Hepatitis C Infection in Special Populations: A Review of the Clinical Evidence and Guidelines*). Studies selected for this review were RCTs comparing boceprevir plus PegIFN α /RBV with PegIFN α /RBV in patients with chronic hepatitis C viral infection co-infected with HIV.

Patient Input Information

The following is a summary of information provided by four patient groups that responded to the CDR call for patient input in the 2011 CDR review of boceprevir:

- Patients indicated that current treatment – PegIFN α /RBV for 24 to 48 weeks – is burdensome due to the large time commitment and side effects; patients also expressed the desire for affordable treatments that would provide faster response rates. Patients expect that less time on treatment would mean enduring side effects for a shorter period of time.
- For patients with advanced disease, the following symptoms were noted to adversely affect quality of life: chronic fatigue, cognitive decline, mood swings, and pain.
- Patients indicated that symptoms of the disease and side effects of current treatment can leave patients unable to contribute to their families financially, stress family relationships, and result in social isolation.
- Patients noted the desire for treatments to be made available early in the disease process, which they expect will result in better treatment responses and a lower risk of future liver cancer compared with delayed treatment. Patients noted that limiting boceprevir treatment to those who have previously failed PegIFN α /RBV would decrease the quality of life for such patients because treatment side effects would be experienced for longer.
- Patients noted that there is a need for treatments for people co-infected with HIV and HCV.

Clinical Trials

The 2011 systematic review of boceprevir included three double-blind RCTs of patients with chronic hepatitis C genotype 1 infection. Patients in the SPRINT-2 trial (N = 1,099) were treatment-naïve, with a minimum HCV RNA level of 10,000 IU/mL. Patients in the RESPOND-2 trial (N = 404) and Study 5685 (N = 201) were treatment-experienced, but were either non-responders to a minimum 12-week course of PegIFN α /RBV (decrease in HCV RNA, but not to undetectable levels) or had relapsed on PegIFN α /RBV (undetectable HCV RNA at the end of treatment, but detectable during follow-up). Prior null responders to PegIFN α /RBV (< 2 log₁₀ decline in HCV RNA at week 12) were excluded. In all three trials, approximately 60% of

patients were HCV genotype 1a, which is considered more refractory to PegIFN α /RBV than genotype 1b. Few patients in SPRINT-2 (5%) and RESPOND-2 (12%) had cirrhosis at baseline; this characteristic was not reported for Study 5685.

All trials included a four-week run-in period during which all patients received PegIFN α /RBV followed by a randomized treatment period of up to 44 weeks. SPRINT-2 and RESPOND-2 randomized patients to boceprevir 800 mg three times daily or placebo, both added onto PegIFN α /RBV. Two boceprevir treatment groups were included in each trial; patients in one boceprevir treatment group were to continue their treatment for 44 weeks, while patients in the other boceprevir treatment group received “response-guided therapy” in which early viral response allowed for early discontinuation of therapy (following 24 weeks and 32 weeks of boceprevir treatment in SPRINT-2 and RESPOND-2, respectively). Study 5685 randomized patients to boceprevir 800 mg three times a day or placebo for 44 weeks, both added onto PegIFN α -2a/RBV. Study 5685 did not have a response-guided therapy group. Details of Study 5685 were limited to information available from a poster abstract.

All trials included a 24-week follow-up period after treatment completion or discontinuation for any reason to assess SVR. The percentage of patients completing 24 weeks of follow-up was similar for all treatment groups in RESPOND-2 (approximately 90%) but was higher for boceprevir groups, compared with placebo, in SPRINT-2 (approximately 90% versus 77%) and Study 5685 (85% versus 39%).

Outcomes

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

- SVR – defined as undetectable HCV RNA for 24 weeks after completion of therapy; the primary outcome in each study.
- Relapse – defined as undetectable HCV RNA at the end of treatment but detectable HCV RNA at end of follow-up.
- Health-related quality of life – investigated in SPRINT-2 and RESPOND-2 using the European Quality of Life-5 Dimension questionnaire (EQ-5D) tool (both visual analogue scale and health state index).
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

Efficacy

- In all three trials, the percentage of patients achieving SVR was statistically significantly greater for patients randomized to a 44-week treatment with boceprevir compared with placebo; 66% versus 38% for treatment-naïve patients (SPRINT-2), and 66% versus 21% and 64% versus 21% for patients with a history of non-response or relapse on PegIFN α /RBV (RESPOND-2 and Study 5685, respectively).
- The frequency of SVR achievement was statistically significantly greater for patients randomized to boceprevir response-guided therapy compared with placebo in both treatment-naïve patients (63% versus 38% based on 24-week response-guided therapy in SPRINT-2) and in patients with a history of non-response or relapse on PegIFN α /RBV (59% versus 21% based on 32-week response-guided therapy in RESPOND-2).
- In both SPRINT-2 and RESPOND-2, the percentage of boceprevir-treated patients achieving SVR was consistently higher for patients who received erythropoietin compared with those who did not.

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- Quality-of-life outcome measures were similar for both boceprevir and placebo treatment groups in the two trials that included this outcome (SPRINT-2 and RESPOND-2). There was a high proportion of patients not providing data at the end of treatment, and quality of life appeared to decline to a similar extent in both boceprevir and placebo groups.
- No data regarding clinically important complications of chronic hepatitis C infection (e.g., cirrhosis, liver transplant, or hepatocellular carcinoma) were available from any of the three studies.

Harms (Safety and Tolerability)

- Withdrawal due to adverse events was similar in the three treatment groups in SPRINT-2; 12% of placebo-treated patients compared with 14% and 10% of boceprevir and boceprevir–response-guided therapy groups, respectively. In RESPOND-2, withdrawal due to adverse events was statistically significantly higher in the boceprevir group (12%) compared with placebo (1%) but not statistically significantly different between boceprevir response-guided therapy (6%) and placebo.
- Anemia was the most common adverse event in both SPRINT-2 and RESPOND-2, and the percentage of patients with anemia was higher for boceprevir groups (including response-guided therapy) compared with placebo, in both trials.
- In both SPRINT-2 and RESPOND-2, the percentage of patients who received erythropoietin to manage treatment-related anemia was approximately two-fold higher for patients treated with boceprevir (including response-guided therapy) compared with placebo.
- Suicidal ideation occurred in four patients treated with boceprevir in SPRINT-2 and five patients (including three in the response-guided therapy group) in RESPOND-2 compared with one patient treated with placebo, across these two studies.

Cost and Cost-Effectiveness

In the 2011 CDR review of boceprevir, the manufacturer submitted two cost-utility analyses for patients with chronic hepatitis C representing those who are treatment-naïve and treatment-experienced to compare boceprevir plus PegIFN α /RBV–response-guided therapy with PegIFN α /RBV alone. The efficacy of boceprevir plus PegIFN α /RBV–response-guided therapy compared with PegIFN α /RBV alone was derived from the SPRINT-2 (treatment-naïve) and RESPOND-2 (treatment-experienced) studies. Data on adverse events (e.g., anemia) were also obtained from SPRINT-2 and RESPOND-2. Based on patient attributes and SVR rates, the cumulative incidence of complications (decompensated cirrhosis, hepatocellular carcinoma, liver transplant, death, and post-liver transplant) during patients’ lifetimes were forecasted using published rates of progression among individuals with chronic hepatitis C infection. The models assume that those obtaining SVR are essentially cured and do not progress to develop complications. Health state utility values (to calculate QALYs) for all states in the model were derived from a single Canadian study. The costs to manage chronic hepatitis C and its associated complications were derived from a published CADTH health technology assessment 2007 report on chronic HCV infection. The manufacturer reported that boceprevir plus PegIFN α /RBV response-guided therapy compared with PegIFN α /RBV alone resulted in a cost per QALY of \$36,712 in patients who are treatment-naïve and \$32,143 per QALY in patients who are treatment-experienced.

CDR noted a number of limitations with the manufacturer’s submission. The manufacturer made assumptions around utility values, transition probabilities, SVR cure rates, and treatment duration, which bias results in favour of boceprevir. In addition, the manufacturer did not

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consider subgroups in the cost-effectiveness analyses. CDR observed notable differences in cost per QALY estimates after adjusting for sources of uncertainty (utility values, transition probabilities, SVR cure rates, treatment duration) and for different patient populations (by patient age and degree of liver fibrosis). When more conservative model inputs were applied, cost per QALY values for boceprevir increased in excess of \$100,000 per QALY, particularly in patients with a low degree of liver fibrosis.

At recommended doses, boceprevir costs between \$25,200 to \$46,200 for one 24 to 44-week course of therapy (not including the cost of PegIFN α /RBV or erythropoietin). One 24 to 48-week course of boceprevir plus PegIFN α /RBV therapy (\$36,837 to \$66,148) is more expensive than PegIFN α /RBV alone (\$9,026 to 19,948), peginterferon monotherapy (\$19,000), and interferon monotherapy (\$5,041 to \$9,147).

Other Discussion Points:

CDEC noted the following:

- A proportion of patients infected with HCV will spontaneously clear the infection, suggesting that patients who were diagnosed with chronic hepatitis C more than six months previously should undergo additional testing to confirm the presence of detectable levels of HCV RNA.
- A large percentage of patients with chronic HCV infection will not develop progressive liver disease, and that treatments for chronic hepatitis C have substantial potential for harm. CDEC also noted the high cost of boceprevir treatment and cost-effectiveness estimates that are less favourable in patients with low fibrosis scores. CDEC further noted that the balance of benefits and harms suggest that patients with higher fibrosis scores are a priority for treatment.
- SVR, a surrogate outcome, was the primary outcome in all reviewed trials, and that there are observational data to support the use of SVR as a surrogate for future liver-related morbidity and mortality.
- Erythropoietin, which was commonly used to manage treatment-related anemia in SPRINT-2 and RESPOND-2, is not reimbursed for this purpose by all publicly-funded drug plans in Canada.
- The cost of boceprevir greatly exceeds that of protease inhibitors used for other indications.
- Compared with HCV infection alone, co-infection with HIV and HCV is associated with an increased risk of hepatic complications.
- Evidence regarding the safety and efficacy of boceprevir in patients co-infected with HIV and HCV is limited to a single phase 2 RCT and the cost-effectiveness of boceprevir in this patient population has not been assessed.

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.

Regrets:

September 21, 2011: One CDEC member did not attend.

May 15, 2013: None

Conflicts of Interest:

September 21, 2011: One CDEC member did not vote.

May 15, 2013: 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 in conformity with the *CDR Confidentiality Guidelines*.

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