CDEC FINAL RECOMMENDATION

BOCEPREVIR
(Victrelis – Merck Canada Inc.)
Indication: Hepatitis C, Chronic

Recommendation:
The Canadian Drug Expert Committee (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 (PegIFNα)/ribavirin (RBV), if all of the following criteria are met:

- a reduced price
- detectable levels of hepatitis C virus (HCV) RNA in the last six months
- a fibrosis stage, based on liver biopsy, of F2, F3, or F4
- patient not co-infected with HIV
- 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 PegIFNα/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-naive patients, and patients who had either not had an adequate response or had relapsed after previous PegIFNα/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 PegIFNα/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.

Of Note:

1. The Committee noted that the cost of boceprevir greatly exceeds that of protease inhibitors used for other indications.

2. The Committee 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.
3. The Committee noted that the product monograph recommends discontinuation of therapy in all patients with:
    - HCV RNA levels ≥ 100 IU/mL at treatment week 12, or
    - Confirmed detectable HCV RNA levels at treatment week 24.
4. Patients with HIV infection were excluded from reviewed trials.
5. There are no RCTs which examine the clinical benefit of repeated courses of boceprevir in patients with chronic hepatitis C infection.

Background:
Boceprevir has a Health Canada indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with PegIFNα/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 Health Canada approved dose is 800 mg three times daily. The product monograph states that boceprevir should not be used as monotherapy, but only in combination with PegIFNα/RBV.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review 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 PegIFNα/RBV (decrease in HCV RNA, but not to undetectable levels) or had relapsed on PegIFNα/RBV (undetectable HCV RNA at end of treatment, but detectable during follow-up). Prior null responders to PegIFNα/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 PegIFNα/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 PegIFNα/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 on to PegIFNα-2b/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 on to PegIFNα-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, the Committee discussed the following: SVR, relapse, quality of life, and adverse events.

The primary outcome in each study was SVR, defined as undetectable HCV RNA for 24 weeks after completion of therapy. Relapse was defined as undetectable HCV RNA at end of treatment but detectable HCV RNA at end of follow-up.

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.

Results

Efficacy or Effectiveness

- In all three trials, the percentage of patients achieving SVR was statistically significantly greater for patients randomized to 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 PegIFNα/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 PegIFNα/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 to those who did not.
- 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.

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 that 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

The manufacturer submitted two cost-utility analyses for patients with chronic hepatitis C who are: 1) treatment naïve; and 2) treatment experienced; to compare boceprevir plus PegIFNα/RBV– response-guided therapy with PegIFNα/RBV alone. The efficacy of boceprevir plus PegIFNα/RBV–response-guided therapy compared with PegIFNα/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) over 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 hepatitis C virus infection. The manufacturer reported that boceprevir plus PegIFNα/RBV response-guided therapy compared with PegIFNα/RBV alone resulted in a cost per QALY of $36,712 in patients who are treatment-naive 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 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 PegIFNα/RBV or erythropoietin). One 24- to 48-week course of boceprevir plus PegIFNα/RBV therapy ($36,837 to $66,148) is more expensive

than PegIFNα/RBV alone ($9,026 to 19,948), peginterferon monotherapy ($19,000), and interferon monotherapy ($5,041 to $9,147).

Patient Input Information:
The following is a summary of information provided by four patient groups who responded to the CDR Call for Patient Input:

- Patients indicated that current treatment, PegIFNα/RBV for 24-48 weeks, is burdensome due to the high time commitment and side effects; patients 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, stressing family relationships, and resulting in social isolation.
- Patients expressed 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 PegIFNα/RBV would decrease the quality of life for such patients because treatment side effects would be experienced for longer.

Other Discussion Points:

- The Committee noted that 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.
- The Committee noted that 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. The Committee further noted the high cost of boceprevir treatment and cost-effectiveness estimates that are less favourable in patients with low fibrosis scores. The Committee discussed that the balance of benefits and harms suggest that patients with higher fibrosis scores are a priority for treatment.
- The Committee discussed that 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.
- The Committee noted that boceprevir is the first direct-acting antiviral agent approved by Health Canada for the treatment of chronic hepatitis C.
- The Committee noted that erythropoietin, which was commonly used to manage treatment-related anemia in SPRINT-2 and RESPOND-2, is not reimbursed for this purpose by all publically funded drug plans in Canada.

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:
One CDEC member did not vote due to considerations of conflict of interest.

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 not 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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