Canadian Drug Expert Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Victrelis, which is also called boceprevir, be listed by Canada's publicly funded drug plans for the treatment of chronic hepatitis C genotype 1 infection in patients with compensated (adequately corrected) liver disease, in combination with peginterferon alpha (PegIFNα)/ribavirin (RBV), if all of the following criteria are met:

- a reduced price
- measurable levels of hepatitis C virus (HCV) RNA in the last six months
- a fibrosis (scarring and thickening of tissue) stage, based on liver biopsy, of F2, F3, or F4
- patient not also infected with HIV
- one course of treatment only (up to 44 weeks duration).

Reasons for the Recommendation:
1. In three medical studies comparing placebo (a capsule containing no active medication) with Victrelis, both used in combination with PegIFNα/RBV, a higher percentage of patients on Victrelis reached a sustained virologic response (SVR). The benefit of Victrelis was seen both in patients who had not had treatment before, as well as in patients who had not improved enough, or who had worsened after improvement, on previous PegIFNα/RBV treatment.

2. At the submitted price, Victrelis costs between $25,200 and $46,200 for one 24- to 44-week course of therapy, not including the cost of PegIFNα/RBV or erythropoietin. There was a lot of uncertainty around the estimates of cost-effectiveness for Victrelis, but cost-effectiveness estimates were higher (that is, less cost-effective) for patients with a low amount of liver fibrosis.

Of Note:
1. The Committee noted that the cost of Victrelis is much greater than that of protease inhibitors used to treat other disease conditions.

2. The Committee considered response-guided therapy (treatment duration based upon the response of the patient) to be more cost-effective than a full course of therapy (44 weeks of Victrelis), in patients for whom response-guided therapy is appropriate.
3. The Committee noted that the product monograph recommends that treatment should be stopped in all patients with:
    - HCV RNA levels ≥ 100 IU/mL at treatment week 12, or
    - Confirmed measurable HCV RNA levels at treatment week 24.
4. Patients with HIV infection were not included in the reviewed studies.
5. There are no good-quality studies that looked at the benefit to patients with chronic hepatitis C infection of having more than one course of treatment with Victrelis.

Background:
Victrelis belongs to a class of drugs called HCV protease inhibitors. It works by directly targeting HCV to reduce the amount of virus in the body. Patients with hepatitis C have the virus in their blood and in their liver. Victrelis is approved by Health Canada 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 (a type of inflammation between the liver cells), who are previously untreated or who have failed previous therapy.

Victrelis is available as 200 mg capsules, and the Health Canada–approved dose is 800 mg three times daily. The product monograph states that Victrelis should not be used by itself but only together with PegIFNα/RBV.

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 Victrelis and a review of economic information prepared by the manufacturer of Victrelis. Also, CDEC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated, or who might use the drug.

Clinical Trials
The Committee reviewed three medical studies of patients with chronic hepatitis C genotype 1 infection. Patients in SPRINT-2 (with 1,099 patients) had never had treatment before and had a HCV RNA level of at least 10,000 IU/mL. Patients in RESPOND-2 (with 404 patients) and study 5685 (with 201 patients) had previously been treated, but had either not improved enough on a 12-week or longer course of PegIFNα/RBV (decrease in HCV RNA, but levels of the virus still measurable), or had become worse again on PegIFNα/RBV (unmeasurable levels of virus at end of treatment, but measurable during follow-up). Patients who did not improve at all after 12 weeks of treatment with PegIFNα/RBV were not included. In all three studies, approximately 60% of patients were HCV genotype 1a, a type of virus that is harder to treat with PegIFNα/RBV than is genotype 1b. Few patients in SPRINT-2 (5%) and RESPOND-2 (12%) had cirrhosis at study start; the percentage of patients with cirrhosis in study 5685 was not reported.

At the beginning of each study, there was a four-week period in which patients received PegIFNα/RBV; after this, patients received their study medication for up to 44 additional weeks. Patients in SPRINT-2 and RESPOND-2 received either Victrelis 800 mg three times daily or placebo, both added onto PegIFNα-2b/RBV. Two Victrelis-treatment groups were included in

each trial; patients in one Victrelis-treatment group were to continue their treatment for 44 weeks, while patients in the other Victrelis-treatment group received "response-guided therapy", meaning that if they responded, treatment would be stopped early (following 24 weeks and 32 weeks of Victrelis treatment in SPRINT-2 and RESPOND-2, respectively).

Patients in study 5685 received either Victrelis 800 mg three times a day or placebo for 44 weeks, both added onto PegIFNα-2a/RBV. Patients in study 5685 did not have a response-guided therapy group. Not many details of study 5685 were available (a poster abstract only).

All studies had a 24-week follow-up period after treatment was finished or stopped for any reason to assess SVR. The percentage of patients who finished 24 weeks of follow-up was similar for all treatment groups in RESPOND-2 (approximately 90%), but was higher for Victrelis groups, compared with placebo, in SPRINT-2 (approximately 90% versus 77%) and study 5685 (85% versus 39%).

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: SVR, relapse (worsening after an improvement), quality of life, and side effects.

The main purpose of each study was to determine the percentage of patients who achieved SVR, defined as unmeasurable HCV RNA for 24 weeks after finishing treatment. Relapse was defined as unmeasurable HCV RNA at end of treatment, but measurable HCV RNA at end of follow-up.

No data regarding important complications of chronic hepatitis C infection (e.g., cirrhosis, liver transplant, or liver cancer) were available from any of the three studies.

Results

Efficacy or Effectiveness

- In all three studies, the percentage of patients achieving SVR was greater for patients in the Victrelis (44-week treatment) groups, compared with the placebo groups: 66% versus 38% for patients who had not previously been treated (SPRINT-2), and 66% versus 21% and 64% versus 21% for patients with not enough improvement or worsening after improvement on PegIFNα/RBV (RESPOND-2 and study 5685, respectively).
- The percentage of patients achieving SVR was greater for patients in the Victrelis-response-guided therapy groups compared with placebo, regardless of whether they had not been treated before (63% versus 38%, based on 24-week response-guided therapy in SPRINT-2), or whether they had not improved enough or had worsening after improvement 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 Victrelis-treated patients reaching SVR was greater for patients who received erythropoietin compared with those who did not.
- Quality of life outcome measures were similar for both Victrelis and placebo treatment groups in the two studies that included this outcome (SPRINT-2 and RESPOND-2). There was a high proportion of patients who did not provide data at the end of the treatment, and quality of life seemed to decrease about the same for both Victrelis and placebo groups.

Harms (Safety and Tolerability)

- In SPRINT-2, similar percentages of patients stopped taking part in the study due to side effects, regardless of which of the three treatments the patients received: 12% of placebo-treated patients, compared with 14% and 10% of Victrelis and Victrelis-response-guided therapy groups, respectively. In RESPOND-2, a greater percentage of patients in the Victrelis group (12%) compared with that in the placebo group (1%) stopped taking part in the study because of side effects. However, in the same study there was not much difference between Victrelis-response-guided therapy (6% of patients stopping participation due to side effects) and placebo.
- Anemia (low red blood cell count) was the most common side effect in both SPRINT-2 and RESPOND-2, and the percentage of patients with anemia was higher for Victrelis groups (including response-guided therapy) compared with that of placebo groups in both studies.
- In both SPRINT-2 and RESPOND-2, the percentage of patients who received erythropoietin to help improve the anemia from treatment was approximately twice as high for Victrelis patients (including response-guided therapy) compared with placebo patients.
- Thoughts of suicide occurred in four patients treated with Victrelis 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 economic information to compare Victrelis plus PegIFNα/RBV response-guided therapy with PegIFNα/RBV alone, to evaluate the health benefit. The analysis was done for patients who had not had previous treatment, as well as for patients who had already had treatment for chronic hepatitis C. Data regarding the efficacy and safety of Victrelis were taken from SPRINT-2 and RESPOND-2 study results. The likelihood of patients experiencing the complications of hepatitis C infection (e.g., worsened cirrhosis, liver cancer, liver transplant, and death) over their lifetime was forecast using other published information. Information on quality of life came from one Canadian study, and treatment costs for managing chronic hepatitis C and its complications were derived from a published 2007 CADTH Health Technology Assessment report.

CDR noted a number of potential problems with the manufacturer's submission, including some assumptions that bias results in favour of Victrelis. In addition, the manufacturer did not consider subgroups in its cost-effectiveness analyses. There was a lot of uncertainty regarding the estimates of cost-effectiveness for Victrelis, but cost-effectiveness estimates were higher (that is, less cost-effective) for patients with a low amount of liver fibrosis.

At recommended doses, Victrelis costs between $25,200 and $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 Victrelis 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 used alone ($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 to 48 weeks, is very difficult as it takes a lot of time and there are side effects; patients wished to have affordable treatments available that would work faster. Patients expect that less time on treatment would mean that they would not have to put up with side effects for as long.
- For patients with advanced disease, the following symptoms decreased their quality of life: chronic fatigue, decreased ability to think and reason, mood swings, and pain.
- Patients pointed out 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 wished that treatments would 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 Victrelis 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 HCV infection can clear on its own in a proportion of infected patients, and therefore patients who were diagnosed with chronic hepatitis C more than six months previously should undergo additional testing to see whether HCV RNA is still there.
- The Committee noted that a large percentage of patients with chronic HCV infection will not develop worsening liver disease, and that treatments for chronic hepatitis C have a high potential for harm. The Committee further noted the high cost of Victrelis treatment and cost-effectiveness estimates that are less favourable in patients who have low fibrosis scores. The Committee discussed the balance of benefits and harms which suggest that patients with higher fibrosis scores are a priority for treatment.
- The Committee discussed that there are observational studies that suggest that whether or not patients achieve SVR may be used to predict whether or not patients will experience future liver-related disease and death.
- The Committee noted that Victrelis 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
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 not requested the deletion of any confidential information.