



CDEC FINAL RECOMMENDATION

TELAPREVIR

(Incivek – Vertex Pharmaceuticals Inc.)

Indication: Hepatitis C, Chronic

This recommendation supersedes the Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated February 15, 2012.

Recommendation:

CDEC recommends that telaprevir 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

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

Conditions:

1. a reduced price
2. one course of treatment only (12 weeks duration).

Reasons for the Recommendation:

1. In five double-blind randomized controlled trials (RCTs), of either treatment-naïve (three trials) or treatment-experienced (two trials) patients treated with concomitant PegIFN α /RBV, a statistically significantly higher percentage of telaprevir-treated patients achieved a sustained virologic response (SVR) compared with placebo.
2. At the submitted price, telaprevir costs approximately \$34,968 per 12-week course of therapy, not including the cost of PegIFN α /RBV. At this price, the total cost of telaprevir therapy (12 weeks, plus PegIFN α /RBV for 24 to 48 weeks) is between \$45,000 and \$55,000, which is more than double the cost of the PegIFN α /RBV combination alone (\$19,800; 48-week treatment).
3. There was considerable uncertainty around the cost-effectiveness estimates for telaprevir supplied by the manufacturer. When conservative model inputs were considered in Common Drug Review (CDR) reanalyses, cost per quality-adjusted life-year (QALY) values increased in excess of \$50,000 for most patient populations, with the exception of patients with prior relapse.

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Of Note:

1. A substantial price reduction is needed to justify the additional costs associated with the use of telaprevir, an add-on therapy to PegIFN α /RBV.
2. CDEC noted that the response-guided therapy recommended in the telaprevir product monograph, allowing for a shortened PegIFN α /RBV treatment duration (24 weeks), would be less costly than a full course of therapy, in patients for whom response-guided therapy is appropriate.
3. CDEC noted that the product monograph recommends discontinuation of therapy in all patients with:
 - HCV RNA levels > 1,000 IU/mL at treatment week four or week 12, or
 - Confirmed detectable HCV RNA levels at treatment week 24.
4. There are no RCTs that examine the clinical benefit of repeated courses of HCV protease inhibitors in patients with chronic hepatitis C infection. Thus, there is no evidence to support repeated or sequential courses of these agents.
5. CDEC concluded that the balance of benefits and harms suggests that patients with higher fibrosis scores should be a priority for treatment.
6. Patients co-infected with HIV and HCV were excluded from the RCTs that were included in the 2012 CDR review of telaprevir. CDEC noted that the use of telaprevir in patients co-infected with HIV and HCV continues to be investigated and that telaprevir 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.
7. In both the ADVANCE and REALIZE 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:

Telaprevir, in combination with PegIFN α /RBV, has a Health Canada indication for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naive or who have previously been treated with interferon-based treatment, including null responders, partial responders, and relapsers. Telaprevir is a protease inhibitor. It is available as 375 mg tablets and the recommended dose is 750 mg taken orally three times a day. The product monograph states that telaprevir must 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 with telaprevir has not been established in patients co-infected with HIV and HCV.

Submission History:

In February 2012, CDEC recommended that telaprevir 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 with regard to 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 telaprevir in patients co-infected with HIV and HCV, CDEC was asked to clarify if there is a role for telaprevir in this patient population.

Summary of CDEC Considerations:

CDEC considered the following information from the 2012 review of telaprevir:

- A systematic review of double-blind RCTs
- A critique of the manufacturer’s pharmaco-economic evaluation
- Patient group-submitted information.

CDEC considered the following to address the request for advice:

- Materials included in the CDEC brief for the 2012 review of telaprevir.
- The original CDEC recommendation for telaprevir (February 15, 2012).
- 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 telaprevir plus PegIFN α /RBV with PegIFN α /RBV in patients with chronic HCV infection co-infected with HIV.

Patient Input Information

The following is a summary of information provided by three patients groups that responded to the CDR call for patient input in the 2012 CDR review of telaprevir:

- Patients indicated that the duration of current treatments for chronic hepatitis C infection is burdensome, particularly related to the long time period over which side effects must be endured. Patients expressed the desire for shorter treatment durations.
- Patients who have not cleared the virus using current therapy believe that telaprevir provides new hope for a cure.
- Patients’ main concern was rash, although this was not seen as a reason to stop therapy.
- Patients noted the desire for treatments to be made available early in the disease process.
- Patient groups noted that treatments for people co-infected with HIV and HCV are needed.

Clinical Trials

The 2012 systematic review of telaprevir included five double-blind RCTs of patients with chronic hepatitis C genotype 1 infection. The main studies were two phase 3 trials (ADVANCE and REALIZE). Patients in ADVANCE were treatment naive with an HCV RNA level of $\geq 1,000$ IU/mL. Patients in REALIZE were treatment experienced with an HCV RNA level of $\geq 1,000$ IU/mL, including null responders to a minimum 12-week course of PegIFN α /RBV

(< 2 log₁₀ decrease in HCV RNA at week 12), partial responders (≥ 2 log₁₀ decrease in HCV RNA at week 12, but not to undetectable levels) or those who had relapsed (undetectable HCV RNA at end of treatment but detectable during follow-up). Of the three phase 2 trials, two (Studies 104 and 104 EU) exclusively enrolled treatment-naive patients, and one (PROVE-3) exclusively enrolled treatment-experienced patients who were non-responders.

Details of the five trials are presented below. There were no run-in periods in the included studies except in one treatment group of REALIZE, in which all patients received four weeks of PegIFNα/RBV before telaprevir treatment was started (delayed start).

- ADVANCE (N = 1,095) randomized patients to one of three treatment groups: telaprevir 750 mg every eight hours (for eight or 12 weeks), or placebo, all in combination with PegIFNα/RBV. Total duration of PegIFNα/RBV treatment was 24 or 48 weeks, depending upon response.
- REALIZE (N = 662) randomized patients to one of three treatment groups: telaprevir 750 mg every eight hours for 12 weeks (either immediate or delayed start), or placebo, all in combination with PegIFNα/RBV. The total duration of PegIFNα/RBV was 48 weeks.
- PROVE-3 (N = 465) randomized patients to one of four treatment groups: telaprevir (12 weeks) plus PegIFNα/RBV (24 weeks); telaprevir (24 weeks) plus PegIFNα/RBV (48 weeks); telaprevir plus PegIFNα (both 24 weeks); or placebo (24 weeks) plus PegIFNα/RBV (48 weeks). Initial dose for telaprevir was 1,125 mg, then 750 mg every eight hours thereafter.
- Study 104 (N = 250) randomized patients to one of three telaprevir groups or placebo for 12 weeks. The three telaprevir groups differed by the duration of concomitant PegIFNα/RBV therapy: 12, 24, or 48 weeks. Patients randomized to placebo received concomitant PegIFNα/RBV for 48 weeks. Telaprevir dosing was 1,250 mg on Day 1, followed by 750 mg every eight hours.
- Study 104 EU (N = 334) randomized patients to one of four treatment groups: telaprevir plus PegIFNα/RBV (both 12 weeks); telaprevir (12 weeks) plus PegIFNα/RBV (24 weeks); telaprevir plus PegIFNα (both 12 weeks); or placebo (12 weeks) plus PegIFNα/RBV (48 weeks). Telaprevir dosing was 1,250 mg on Day 1, followed by 750 mg every eight hours.

Anemia was typically managed by reducing the dose of ribavirin. If ribavirin had to be stopped, then the telaprevir was also stopped. Telaprevir dose reductions were prohibited, and once telaprevir was discontinued due to anemia or safety, it could not be restarted. Erythropoietin use was not permitted in any of the included studies.

In ADVANCE, 93% patients eligible to 24 weeks total duration of therapy (12 weeks of telaprevir and 24 weeks of PegIFNα/RBV) completed the treatment as assigned by the protocol. However, of those assigned to 48 weeks of treatment (12 weeks of telaprevir and 48 weeks of PegIFNα/RBV), 47% completed the treatment. In REALIZE, 62% and 70% of patients randomized to telaprevir (immediate and delayed start respectively) completed treatment; however only 38% of patients randomized to placebo completed study treatment.

Outcomes

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

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- SVR – the primary outcome in each study; defined as undetectable HCV RNA for 24 weeks after completion of therapy.
- Relapse – defined as undetectable HCV RNA at end of treatment but detectable HCV RNA at end of follow-up.
- Health-related quality of life – assessed in two studies (ADVANCE and REALIZE) using the European Quality of Life – 5 Dimension questionnaire (EQ-5D).
- Total adverse events, serious adverse events, and withdrawal due to adverse events.

Results

CDEC focused its discussion on the results of phase 3 trials and on treatment groups receiving the recommended duration of telaprevir (12 weeks).

Efficacy

- In all trials, the proportion of patients achieving SVR was statistically significantly higher for telaprevir compared with placebo: 75% versus 44% for treatment-naive patients in ADVANCE, and 64% and 66% (immediate and delayed start, respectively) versus 16% for treatment-experienced patients (including, those with prior relapse, prior partial response, and prior null response) in REALIZE.
- Preplanned subgroup analysis, by prior response in REALIZE, revealed statistically significantly higher frequencies of SVR achievement for telaprevir versus placebo, regardless of prior response to PegIFN α /RBV treatment. However, patients who had previously relapsed were the most likely to achieve SVR in the trial, and prior null responders were the least likely.
- Post hoc analyses suggested that the benefit of telaprevir compared with placebo is maintained regardless of baseline fibrosis stage.
- The percentage of patients experiencing treatment relapse was lower with telaprevir regimens compared with placebo.
- Quality of life tended to worsen while patients were on therapy, with minimal differences in quality of life between telaprevir and placebo.
- 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 trials.

Harms (Safety and Tolerability)

- More telaprevir-treated patients experienced a serious adverse event than placebo-treated patients in REALIZE (7% and 6% versus 3%) and ADVANCE (5% versus 2%); the difference was statistically significant in ADVANCE. Anemia and rash were the most common serious adverse events, which occurred more frequently in telaprevir-treated patients.
- There were no noticeable differences between telaprevir and placebo in terms of the percentage of patients experiencing an adverse event in any of the trials.
- Withdrawal due to an adverse event occurred in less than 2% of patients in the ADVANCE and REALIZE studies, with no noticeable differences between the telaprevir and placebo groups. Withdrawal due to an adverse event was more frequent in the phase 2 studies, with the highest frequency in patients treated with telaprevir for 24 weeks: 26% for telaprevir compared with 4% for placebo in the PROVE-3 study.

Cost and Cost-Effectiveness

In the 2012 CDR review of telaprevir, the manufacturer submitted a cost-utility analysis comparing telaprevir plus PegIFN α /RBV with PegIFN α /RBV alone for patients with HCV infection with genotype 1 according to their treatment history and prior response, including treatment naive, prior null response, prior partial response, and prior relapse. Efficacy data, in terms of SVR, were derived from ADVANCE for treatment-naive and REALIZE for treatment-experienced patients. The cumulative incidence of HCV complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) over a patient's lifetime was forecasted using published rates of progression among individuals with chronic hepatitis C infection. The analyses assume that those obtaining sustained SVR are essentially cured and do not progress to develop any complications. Data on adverse events (e.g., anemia, rash) and health care consequences were obtained from ADVANCE and REALIZE, although the cost of erythropoietin was not incorporated. Health state utility values for all relevant states in the model were derived from ADVANCE and REALIZE (treatment phase) and published literature (post-treatment phase), whereas the costs to manage hepatitis C and its associated complications were derived from published sources. The manufacturer reported that telaprevir plus PegIFN α /RBV compared with PegIFN α /RBV results in cost per QALY estimates of \$21,901 (treatment naive), \$36,255 (prior null response), \$21,579 (prior partial response), and \$1,467 (prior relapse).

CDR noted a number of limitations with the manufacturer's submission. The manufacturer made assumptions around utility values, transition probabilities, HCV management costs, time horizon, and treatment duration which favour telaprevir and for which the model is sensitive. Results were also sensitive to patient populations (e.g., degree of liver fibrosis, age). When more conservative model inputs were applied, cost per QALY estimates for telaprevir increased in excess of \$50,000 for all patient populations, except in patients with prior relapse, where incremental cost-utility ratios were less than \$30,000 in the majority of CDR reanalyses.

At recommended doses, telaprevir costs approximately \$34,968 per 12-week course of therapy, and 48-week treatment with PegIFN α /RBV costs \$19,800. The total cost of telaprevir therapy (12 weeks, plus PegIFN α /RBV for 24 to 48 weeks) is between \$45,000 and \$55,000.

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 further testing to confirm the presence of detectable levels of HCV RNA.
- A large proportion of patients with chronic HCV infection will not develop progressive liver disease, and treatments for chronic hepatitis C have a substantial potential for harm.
- The reviewed trials were of too short a duration to assess hepatitis-related mortality and morbidity; however, SVR was considered an acceptable surrogate for these clinically relevant outcomes.
- Cost-effectiveness estimates for telaprevir were more favourable among patients who had a prior relapse.

- There are no RCTs comparing telaprevir with boceprevir, making it difficult to differentiate between the two agents. However, CDEC noted that the benefit of telaprevir, specifically in patients with prior null response, was demonstrated in ADVANCE and REALIZE.
- The cost of telaprevir 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 telaprevir in patients co-infected with HIV and HCV is limited to a single phase 2 RCT and the cost-effectiveness of telaprevir in this patient population has not been assessed. CDEC noted that higher doses of telaprevir could be required in patients treated with efavirenz, which would result in an increased cost.

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:

January 18, 2012: None

May 15, 2013: None

Conflicts of Interest:

January 18, 2012: One CDEC member did not participate in the 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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