



CDEC FINAL RECOMMENDATION

SIMEPREVIR

(Galexos — Janssen Inc.)

Indication: Chronic Hepatitis C Genotype 1 Infection

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that simeprevir, in combination with peginterferon alfa and ribavirin (PegIFN/ribavirin [RBV]), be listed for the treatment of chronic hepatitis C genotype 1 infection in adults with compensated liver disease, if 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
- patients with the NS3 Q80K polymorphism should not be treated with simeprevir.

Conditions:

- patients should have their HCV strain tested for NS3 Q80K polymorphism
- patients have not received a prior full therapeutic course of boceprevir or telaprevir
- reduced price — the drug plan cost for a course of therapy with simeprevir should not exceed the drug plan cost of other currently available direct-acting antiviral drugs.

Reasons for the Recommendation:

1. In five double-blind randomized controlled trials (RCTs), of either treatment-naïve (QUEST-1, QUEST-2, and PILLAR) or treatment-experienced (ASPIRE and PROMISE) patients, a statistically significantly greater proportion of patients treated with simeprevir plus PegIFN/RBV achieved a sustained virologic response (SVR) compared with placebo plus PegIFN/RBV.
2. There is insufficient evidence to suggest that treatment with simeprevir would result in better clinical outcomes than treatment with boceprevir or telaprevir for genotype 1 hepatitis C infection; therefore, the cost for a course of therapy with simeprevir should not exceed the cost of other currently available direct-acting antiviral drugs.
3. There is evidence to suggest that simeprevir is less effective for HCV genotype 1a with Q80K polymorphism.

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Background:

Simeprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with PegIFN and RBV in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with RBV. Simeprevir is available as 150 mg capsules and the recommended dosage is 150 mg orally once a day for 12 weeks in combination with PegIFN/RBV, followed by further PegIFN/RBV therapy. The actual duration of triple and dual therapy is determined by treatment stopping rules and response-guided therapy (RGT) recommendations that are based on treatment history and patient response to treatment.

Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of simeprevir, a critique of the manufacturer's pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

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

- Hepatitis C is a serious and potentially life-threatening liver disease that is contracted through blood-to-blood contact with an infected person.
- Debilitating physical symptoms may develop, such as chronic fatigue, mental confusion, memory loss, and mood swings that can result in job loss and a reliance on disability benefits or social assistance.
- The lives of caregivers and family members are made much more difficult when a loved one has chronic hepatitis C. They often assume greater financial and child-care responsibilities and worry about their own risk of infection. Family break-up is common.
- People living with chronic hepatitis C want early and uncomplicated access to affordable treatments that have tolerable side effects and that cure the disease in patients with all genotypes. They also want treatments that are shorter in duration than current treatment periods and a reduced pill burden. Many are waiting for new IFN-free or RBV-free therapies to avoid the adverse events associated with those drugs.

Clinical Trials

The CDR systematic review included five double-blind RCTs comparing simeprevir with placebo (both in combination with PegIFN/RBV) in adults with genotype 1 HCV. Three of the five studies (QUEST-1 [N = 395], QUEST-2 [N = 393], and PILLAR [N = 386]) were conducted in patients who were treatment-naïve and two studies (ASPIRE [N = 463] and PROMISE [N = 393]) were conducted in patients who were treatment-experienced. In ASPIRE, treatment-experienced patients consisted of null responders, partial responders, and relapsers following at least one course of PegIFN/RBV therapy, while patients in PROMISE were all patients who had relapsed following at least one course of PegIFN/RBV therapy. In all studies, treatment durations were 24 or 48 weeks, with a planned follow-up to week 72.

Based on the dosing recommended in the product monograph, CDEC focused their discussion on the results for simeprevir 150 mg for 12 weeks in combination with PegIFN/RBV therapy for 24 or 48 weeks.

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Outcomes

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

- SVR12 and SVR24 — defined as undetectable plasma HCV RNA at the end of treatment and 12 weeks after the planned end of treatment (SVR12) or 24 weeks after the planned end of treatment (SVR24).
- SVR at 72 weeks — defined as undetectable plasma HCV RNA at 72 weeks.
- Extended rapid virologic response (eRVR) — defined as undetectable plasma HCV RNA levels at weeks 4 and 12 of treatment.
- Viral relapse — defined as detectable plasma HCV RNA during follow-up in patients who had undetectable plasma HCV RNA (< 25 IU/mL) at end of treatment.
- Fatigue Severity Scale (FSS) — a nine-item scale.
- Work Productivity and Activity Impairment (WPAI) – a six-item questionnaire.
- Mortality (all-cause and liver-related).
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

SVR was the primary end point in all trials; however, the time period at which it was measured differed across trials. SVR12 was the primary outcome in QUEST-1, QUEST-2, and PROMISE. SVR24 was the primary outcome in ASPIRE and SVR at 72 weeks was the primary outcome in PILLAR.

Efficacy

Treatment-naive

- In QUEST-1, the proportion of patients achieving SVR12 was 79.5% in the simeprevir group versus 50.0% in the placebo group; the adjusted risk difference (ARD) was 29.3% (95% confidence interval [CI], 20.1% to 38.6%).
- In QUEST-2, the proportion of patients achieving SVR12 was 81.3% in the simeprevir group versus 50.0% in the placebo group; ARD 32.2% (95% CI, 23.3% to 41.2%).
- In PILLAR, the proportion of patients achieving SVR at 72 weeks was 77.9% in the simeprevir group versus 64.9% in the placebo group; ARD 15.4% (95% CI, –1.1% to 32.0%). While the primary end point was not reached, the proportion of patients achieving SVR24 in PILLAR was statistically significantly higher for simeprevir compared with placebo.
- The difference in area under the curve from baseline to week 60 (AUC_{60}) for WPAI was –235.9 (95% CI, –448.3 to –23.4; $P = 0.030$) in QUEST 1 and –282.4 (95% CI, –491.5 to –73.2; $P = 0.008$) in QUEST-2.
- The difference in AUC_{60} for FSS was –20.7 (95% CI, –32.7 to –8.6; $P < 0.001$) in QUEST-1 and –16.7 (95% CI, –29.1 to –4.3; $P = 0.009$) in QUEST-2.

Treatment-experienced

- In ASPIRE, the proportion of patients achieving SVR24 was 66.7% in the simeprevir group versus 22.7% in the placebo group; ARD 49.4% (95% CI, 30.7% to 68.1%).
- In PROMISE, the proportion of patients achieving SVR12 was 79.2% in the simeprevir group versus 36.1% in the placebo group; ARD 43.8% (95% CI, 34.6% to 53.0%).
- The differences in AUC 60 for WPAI and FSS were -547.9 (-751.9 to -343.9 ; $P < 0.001$) and -26.9 (-39.1 to -14.7 ; $P < 0.001$), respectively in PROMISE.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was reported as follows:
 - QUEST 1: 96.2% with simeprevir and 96.6% with placebo
 - QUEST 2: █████ with simeprevir and █████ with placebo
 - PILLAR: 97.4% with simeprevir and 98.7% with placebo
 - ASPIRE: █████ with simeprevir and █████ with placebo
 - PROMISE: 97.3% with simeprevir and 94.0% with placebo.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
 - QUEST 1: 3.8% with simeprevir and 6.2% with placebo
 - QUEST 2: █████ with simeprevir and █████ with placebo
 - PILLAR: 5.2% with simeprevir and 13.0% with placebo
 - ASPIRE: 10.6% with simeprevir and 6.1% with placebo
 - PROMISE: 5.4% with simeprevir and 7.5% with placebo.
- The proportion of patients who withdrew from study treatment due to adverse events was reported as follows:
 - QUEST 1: 3.4% with simeprevir and 3.1% with placebo
 - QUEST 2: █████ with simeprevir and █████ with placebo
 - PILLAR: 2.6% with simeprevir and 3.9% with placebo
 - ASPIRE: 6.1% with simeprevir and 4.5% with placebo
 - PROMISE: 0% with simeprevir and 0% with placebo
- In all studies, the most commonly reported adverse events were fatigue, headache, infections, and infestations.
- Compared with placebo, patients treated with simeprevir had an increased incidence of neutropenia, pruritus, nausea, and photosensitivity during the first 12 weeks of treatment.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis (CUA) comparing simeprevir plus PegIFN/RBV with telaprevir plus PegIFN/RBV, boceprevir plus PegIFN/RBV, and PegIFN/RBV alone for patients with genotype 1 chronic hepatitis C infection for both treatment-naive and treatment-experienced patients, during a lifetime horizon. Efficacy data, in terms of SVR, were derived from manufacturer-funded unpublished network meta-analyses (NMAs). Treatment-naive and treatment-experienced populations were assessed in separate networks. The cumulative incidence of complications and associated costs (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) was forecasted using published rates of progression among individuals with chronic hepatitis C infection. The manufacturer assumed that patients achieving SVR were essentially cured and did not progress to develop complications. Rates of adverse events (anemia, neutropenia, rash, and pruritus)

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were obtained from the NMA. The manufacturer reported that, for treatment-naive patients, simeprevir plus PegIFN/RBV dominated telaprevir plus PegIFN/RBV (lower total costs and greater clinical benefits), and simeprevir plus PegIFN/RBV resulted in an incremental cost-utility ratio (ICUR) of \$5,202 per quality-adjusted life-year (QALY) and \$32,497 per QALY compared with boceprevir plus PegIFN/RBV and PegIFN/RBV alone, respectively. In treatment-experienced patients, simeprevir plus PegIFN/RBV was less expensive but provided fewer QALY compared with telaprevir plus PegIFN/RBV, dominated boceprevir plus PegIFN/RBV, and resulted in an ICUR of \$20,430 per QALY compared with PegIFN/RBV alone.

CDR identified a number of limitations with the manufacturer's analyses:

- The cost-effectiveness of simeprevir plus PegIFN/RBV is largely dependent on the validity of the NMAs. There was a lack of detailed information on the methods and analyses used in the NMAs, which complicated CDR's critical appraisal and led to uncertainty with the ICURs, especially in the treatment-experienced population.
- The cost of therapies is dependent on the proportion of patients eligible to receive a shorter duration of therapy, based on RGT criteria. The manufacturer assumed in their base-case analysis that prior relapsers on telaprevir plus PegIFN/RBV, as well as prior relapsers and partial responders on boceprevir plus PegIFN/RBV, would not be eligible to receive shorter therapy which may differ from current Canadian practice and may overestimate the total cost associated with these regimens.
- For treatment-experienced patients, the manufacturer assumed that SVR rates would not differ across liver fibrosis stages, which is inconsistent with results from clinical trials.
- Without boceprevir plus PegIFN/RBV trial data for the null responder population, the comparative cost-effectiveness of simeprevir plus PegIFN/RBV and boceprevir plus PegIFN/RBV in this population is unknown.

CDR performed additional sensitivity analyses to test the impact of the identified areas of uncertainty:

- In both treatment-naive and treatment-experienced populations, the ICUR of simeprevir plus PegIFN/RBV versus PegIFN/RBV alone was less than \$50,000 per QALY in most scenarios.
- In treatment-naive patients, when lower drug costs were used and RGT criteria were based on a Canadian label, simeprevir plus PegIFN/RBV dominated telaprevir plus PegIFN/RBV, had an ICUR of \$32,147 compared with boceprevir plus PegIFN/RBV, and had an ICUR of \$35,489 compared with PegIFN/RBV alone. Further, when the lower 95% credible interval (CrI) for SVR, obtained from the NMA, for simeprevir plus PegIFN/RBV compared with PegIFN/RBV alone was used, simeprevir plus PegIFN/RBV was dominated by telaprevir plus PegIFN/RBV, had an ICUR of \$1,077,988 compared with boceprevir plus PegIFN/RBV and \$45,319 compared with PegIFN/RBV alone.
- In treatment-experienced patients, when lower drug costs were used and RGT criteria was based on the Canadian label, simeprevir plus PegIFN/RBV was dominated by telaprevir plus PegIFN/RBV, dominated boceprevir plus PegIFN/RBV, and had an ICUR of \$21,240 compared with PegIFN/RBV alone. Further, in a conservative scenario using the bounds of the 95% CrI from the NMA, simeprevir plus PegIFN/RBV was dominated by telaprevir plus PegIFN/RBV and boceprevir plus PegIFN/RBV, and had an ICUR of \$47,279 versus PegIFN/RBV.

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At the submitted price of \$434.55 per 150 mg tablet, the cost of a 12-week course of simeprevir is \$36,502, which is more costly than a 12-week course of telaprevir (\$34,968) or a 24-week or 32-week course of boceprevir (\$25,200 and \$33,600, respectively), but less costly than a 44-week course of boceprevir (\$46,200).

Other Discussion Points:

CDEC noted the following:

- Resistance testing before therapy may identify the patients who will not respond to a given direct-acting antiviral drug, avoiding ineffective regimens and unnecessary costs. The identification and interpretation of resistance testing results continues to evolve.
- Patient enrolment in all trials was based on liver biopsy. The non-invasive diagnostic tests for fibrosis widely used in clinical practice are recognized to be reliable for F0 and F4 (cirrhosis), but less reliable for differentiating intermediate fibrosis grades.
- The therapeutic approach to HCV is evolving rapidly as many highly effective, fully oral regimens of direct-acting antiviral drugs without PegIFN and/or RBV are emerging.

Research Gaps:

CDEC noted that there is limited evidence or an absence of evidence regarding the following:

- Comparative trials of simeprevir with other direct-acting antiviral drugs.
- Long-term outcomes with respect to the impact of triple therapy on fibrosis or hepatocellular carcinoma, liver transplant, and mortality.
- Efficacy and safety data for null responders, partial responders, patients who have undergone a liver transplantation, and patients with HIV co-infection.
- Compliance and toxicities in real-world settings, given that a substantial proportion of HCV patients are parenteral drug users.

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. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

May 21, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

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