

CDEC FINAL RECOMMENDATION

OMBITASVIR/PARITAPREVIR/RITONAVIR and DASABUVIR

(Holkira Pak — AbbVie Corporation)

Indication: Chronic Hepatitis C Virus Genotype 1 Infection in Adults

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/RTV and DSV) be listed for the treatment of adults with genotype 1 chronic hepatitis C virus (CHC) infection, including those with compensated cirrhosis, if the following clinical criterion and conditions are met:

Clinical criterion:

- Liver fibrosis stage of ≥ 2 .

Conditions:

- Treatment should be initiated by physicians with experience in the management of CHC patients.
- Drug plan costs for OBV/PTV/RTV and DSV should not exceed the drug plan costs of other interferon-free regimens for the treatment of CHC.

Reasons for the Recommendation:

1. Six randomized controlled trials (RCTs) (SAPPHIRE I, SAPPHIRE II, PEARL II, PEARL III, PEARL IV, and TURQUOISE II) demonstrated that treatment with OBV/PTV/RTV and DSV achieved high rates of sustained virologic response (SVR) at 12 weeks (SVR12) for both treatment-naïve and treatment-experienced patients with genotype 1 CHC infection with or without ribavirin (RBV).
2. The pharmacoeconomic evaluation suggests that OBV/PTV/RTV and DSV leads to similar quality-adjusted life years (QALYs) as ledipasvir/sofosbuvir (LDV/SOF). In addition, OBV/PTV/RTV and DSV is likely to be associated with an incremental cost-utility ratio within commonly accepted thresholds versus other comparators in those patients who would currently receive pegylated interferon and RBV (PR) therapy. However, jurisdictions will need to consider drug plan and health care system sustainability when making listing decisions for the treatment of CHC infection with the newly available costly treatment regimens.
3. Due to limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of OBV/PTV/RTV and DSV according to liver fibrosis stage, particularly for patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).

Common Drug Review

Background:

Holkira Pak is indicated in Canada for the treatment of CHC genotype 1 infection in adults, including those with compensated cirrhosis. It is a combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir. OBV/PTV/RTV and DSV is composed of two tablets; the first is composed of 12.5 mg OBV, 75 mg PTV, and 50 mg RTV. The second tablet is composed of 250 mg DSV. The recommended dosage regimen is two tablets daily of OBV/PTV/RTV and two tablets daily of DSV, as follows:

- Genotype 1b without cirrhosis: 12 weeks of treatment without concomitant RBV
- Genotype 1a without cirrhosis: 12 weeks of treatment with concomitant RBV
- Genotypes 1a and 1b with cirrhosis: 12 weeks of treatment with concomitant RBV

The product monograph recommends 24 weeks of OBV/PTV/RTV and DSV plus RBV for patients with genotype 1a infection with cirrhosis, who have had a previous null response to PR.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of OBV/PTV/RTV and DSV, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals with CHC infection.

Patient Input Information

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

- CHC infection is a serious and potentially life-threatening disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and death. Patients may experience fatigue; general weakness; abdominal, muscle, or joint pain; itchiness; poor circulation; constipation; nausea; loss of appetite; headaches; disrupted sleep; and jaundice. Cognitive functioning is affected in some patients.
- Patients must cope with the stigma associated with CHC infection and are often reluctant to disclose their hepatitis C virus (HCV) status for fear of rejection and discrimination.
- Spouses and loved ones who care for patients with CHC infection are faced with a substantial burden, as the symptoms of the infection and side effects of treatment can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children.
- OBV/PTV/RTV and DSV is the second therapy to become available on the market that offers an interferon-free option for CHC patients. Interferon-based therapies are limited by adverse effects that can be debilitating.
- The expectations for OBV/PTV/RTV and DSV are that it will address a large gap and unmet patient needs. Although it requires a slightly more complex daily regimen than LDV/SOF, the length of treatment is 12 weeks, equivalent to LDV/SOF and significantly shorter than older regimens. Because of its low toxicity, it is expected that OBV/PTV/RTV and DSV will open up treatment to patients who had contraindications to, or who could not tolerate, interferon-based treatments. Patients see advantages with OBV/PTV/RTV and DSV that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients: higher response rates.
- Patients do not think any patient should be required to undergo and fail a therapy that includes interferon before becoming eligible for an interferon-free therapy. Patients believe

that all patients diagnosed with CHC should be able to access interferon-free treatments and that having to wait for the disease to progress before they become eligible causes needless suffering.

Clinical Trials

The CDR systematic review included six pivotal phase 3 RCTs. Three double-blinded trials included patients who had no previous experience with antiviral treatment for hepatitis C infection (SAPPHIRE I [N = 631], PEARL III [N = 419], and PEARL IV [N = 305]), two trials included patients who had failed previous antiviral treatment (SAPPHIRE II [double-blinded; N = 395] and PEARL II [open-label; N = 389]), and one trial included both treatment-naïve and treatment-experienced patients who had hepatic cirrhosis (TURQUOISE II [open-label; N = 381]). The trials evaluated 12 weeks of treatment with OBV/PTV/RTV and DSV plus RBV relative to OBV/PTV/RTV and DSV alone (three trials) or OBV/PTV/RTV and DSV plus RBV administered for 24 weeks (TURQUOISE II). The included patients had to be free from hepatic cirrhosis at screening in all trials except TURQUOISE II, which exclusively enrolled patients with compensated hepatic cirrhosis. In other respects, all three trials had similar inclusion and exclusion criteria. Patients with significant comorbidities or other active clinical conditions commonly seen in the CHC infection population, most notably hepatitis B virus and HIV co-infection, were excluded in all trials.

Outcomes

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

- SVR12 — defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) 12 weeks after stopping all study drugs.
- Relapse — defined as having HCV RNA greater than or equal to LLOQ during the post-treatment period after having achieved HCV RNA less than LLOQ at the end of treatment, confirmed with two consecutive values or last available post-treatment measurement.
- Short-Form 36-Item Health Survey (SF-36) — a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems. SF-36 also provides two component summaries, the physical component summary and the mental component summary.
- EuroQol 5-Dimensions (EQ-5D) Questionnaire — a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- Hepatitis C Virus Patient-Reported Outcomes Instrument (HCV-PRO) — developed specifically to capture the impact of HCV conditions and treatment upon function and well-being as related to physical, emotional, and social health; productivity; intimacy; and perceptions of overall quality of life in adults. The HCV-PRO contains 16 items with five levels of response choices, ranging from “all of the time” (1) to “none of the time” (5). The HCV-PRO total score is the sum of 16 individual item scores converted to a 0 to 100 scale as follows: $([\text{sum} - 16] \times 100)/64$. A higher HCV-PRO score indicates a better state of health.

Common Drug Review

The primary outcome of all studies was the proportion of patients with SVR12.

Efficacy

- All OBV/PTV/RTV and DSV treatment groups demonstrated statistical superiority compared with the historical control rates for SVR12. The proportions of patients with SVR12 were:
 - SAPPHIRE I: 96.2% for OBV/PTV/RTV and DSV plus RBV (12 weeks) versus 70% historical control rate
 - PEARL III: 99.5% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 99% for OBV/PTV/RTV and DSV without RBV (12 weeks) versus 73% historical control rate
 - PEARL IV: 97.0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 90.2% for OBV/PTV/RTV and DSV without ribavirin (12 weeks) versus 65% historical control rate
 - SAPPHIRE II: 96.3% for OBV/PTV/RTV and DSV plus RBV (12 weeks) versus 60% historical control rate
 - PEARL II: 96.6% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 100% for OBV/PTV/RTV and DSV without RBV (12 weeks) versus 64% historical control rate
 - TURQUOISE II: 91.8% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 95.9% for OBV/PTV/RTV and DSV plus RBV (24 weeks) versus 43% historical control rate.
- The proportions of patients experiencing relapse were:
 - SAPPHIRE I: 1.5% for OBV/PTV/RTV and DSV plus RBV (12 weeks)
 - PEARL III: 0% for both OBV/PTV/RTV and DSV with and without RBV (12 weeks)
 - PEARL IV: 1% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 5.2% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - SAPPHIRE II: 2.4% for OBV/PTV/RTV and DSV plus RBV (12 weeks)
 - PEARL II: 0% for both OBV/PTV/RTV and DSV with and without RBV (12 weeks)
 - TURQUOISE II: 5.9% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0.6% for OBV/PTV/RTV and DSV plus RBV (24 weeks).
- Changes in SF-36, EQ-5D, and HCV-PRO scores showed no statistically significant differences between treatment groups within each trial, and when one instrument showed a difference in one trial, this difference was not consistent with the other instruments. While no clinically meaningful changes occurred during treatment, there was also no substantive deterioration in HRQoL scores during treatment.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one serious adverse event were:
 - SAPPHIRE I: 2.1% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0% for placebo
 - PEARL III: 1.9% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 1.9% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - PEARL IV: 3.0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0.5% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - SAPPHIRE II: 2.0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 1.0% for placebo
 - PEARL II: 2.2% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 2.1% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - TURQUOISE II: 6.3% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 4.7% for OBV/PTV/RTV and DSV plus RBV (24 weeks).

- The most frequently reported adverse events with OBV/PTV/RTV and DSV were fatigue (32% to 46%), headache (23.0% to 36.4%), nausea (11% to 24%), insomnia (9% to 15%), rash (5% to 11%), pruritus (14% to 18%), anemia (5% to 11%), asthenia (1% to 15.8%), diarrhea (4.3% to 16.9%), and rash (1% to 14.5%).
- The proportions of patients who experienced at least one adverse event were:
 - SAPPHIRE I: 87.5% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 73.4% for placebo
 - PEARL III: 80% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 67% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - PEARL IV: 92% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 82.4% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - SAPPHIRE II: 91.2% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 82.5% for placebo
 - PEARL II: 79.1% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 77.9% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - TURQUOISE II: 91.8% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 90.7% for OBV/PTV/RTV and DSV plus RBV (24 weeks).
- The proportions of patients who withdrew from the trial as a result of adverse events were:
 - SAPPHIRE I: 0.6% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0.6% for placebo
 - PEARL III: 0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - PEARL IV: 0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 1.0% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - SAPPHIRE II: 1.0% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0% for placebo
 - PEARL II: 2.2% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 0% for OBV/PTV/RTV and DSV without RBV (12 weeks)
 - TURQUOISE II: 1.9% for OBV/PTV/RTV and DSV plus RBV (12 weeks) and 2.3% for OBV/PTV/RTV and DSV plus RBV (24 weeks).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing OBV/PTV/RTV and DSV with the following: LDV/SOF; sofosbuvir plus PR (SOF + PR); telaprevir plus PR; boceprevir plus PR; and simeprevir plus PR (SIM + PR) in patients with genotype 1 CHC. The analysis was conducted over a patient lifetime (up to 70 years) from a public-payer perspective. The model structure consisted of 10 distinct health states representing mild and moderate fibrosis states, compensated cirrhosis states, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death. Reinfection was considered and the model assumed no re-treatment upon reinfection. The patient cohort was assumed to have a mean age of 52 and consisted of a mixture of cirrhotic and non-cirrhotic patients; separate analyses were undertaken for treatment-naïve (comprising 62.6%, 24.4%, and 11% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; 66.4% with genotype 1a) and treatment-experienced (comprising 47.3%, 23.3%, and 29.4% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; 66.4% with genotype 1a) cohorts. The treatment-experienced cohort was further stratified by the type of prior response: null responders, partial responders, and prior relapses.

Natural history transition rates were derived from published studies. The effectiveness data (i.e., SVR rates) and incidence of specific adverse events (i.e., anemia, rash, depression, neutropenia, and thrombocytopenia) were derived from the active groups of the pivotal trials (using a naive indirect comparison). Utility values for CHC health states and utility decrement associated with each treatment varied and were based on several published sources. Costs and health care resource use were based on published Canadian sources. The cost of RBV was assumed to be \$0.

The manufacturer reported that OBV/PTV/RTV and DSV was either dominant (i.e., less costly and more effective), highly cost-effective, or substantially less expensive than alternative treatments with slightly fewer QALY gains.

CDR identified several limitations with the manufacturer's pharmacoeconomic analysis:

- The effectiveness estimates were from separate non-comparative and potentially non-comparable trials.
- The natural history model was based on publications from 1997 and relatively small studies, while more recent and robust sources were available.
- The treatment-related utility decrement with SOF + PR was likely overestimated.
- The cost of anemia was likely overestimated, which favours OBV/PTV/RTV and DSV due to its lower incidence of anemia.
- The utility data collected in the trial program were not used in the base-case analysis.
- The comparative reinfection rate in patients treated with interferon-free regimens versus those treated with PR-based therapies is unknown and was not properly explored.

CDR reanalyses were unable to account for all of the limitations noted above. CDR reanalyses using a different treatment-related utility decrement for SOF + PR and lower anemia cost showed no significant differences compared with the manufacturer's results, but there remains considerable uncertainty regarding the comparative cost-effectiveness of OBV/PTV/RTV and DSV compared with other treatment regimens. The comparative cost-effectiveness of OBV/PTV/RTV and DSV and LDV/SOF was subject to significant variation, due to the small difference in QALYs, and the results were sensitive to variations in drug price. The manufacturer's pharmacoeconomic analysis does not provide sufficiently robust evidence of the likely cost-effectiveness of OBV/PTV/RTV and DSV in all the various patient groups that are likely to seek treatment for CHC with interferon-free regimens.

At the submitted price of \$[REDACTED] per day, a 12-week course of OBV/PTV/RTV and DSV (\$[REDACTED]) is more expensive than a 24- to 48-week course of SIM + PR (ranging from \$46,002 to \$55,502) and an eight-week course of LDV/SOF (\$44,667), but less expensive than a 12-week course of SOF + PR (\$59,750), a 12-week course of LDV/SOF (\$67,000), or a 24-week course of SOF + RBV (\$116,090 to \$117,308). For patients with genotype 1a with cirrhosis who had previous null response to PR, a 24-week course of OBV/PTV/RTV and DSV (\$[REDACTED]) is more expensive than all other regimens available for that population, with the exception of a 24-week course of LDV/SOF (\$134,000). The price of comparators is based on the list price and is not reflective of product listing agreements.

Other Discussion Points:

CDEC noted the following:

- OBV/PTV/RTV and DSV may offer a greater range of therapeutic options to some patients, but it does not offer greater convenience when compared with LDV/SOF, because of the greater pill burden and the need for twice-daily dosing.
- OBV/PTV/RTV and DSV may have a greater potential for adverse drug–drug interactions than LDV/SOF.
- A phase 2 trial (TURQUOISE I; N = 63) randomized CHC patients co-infected with HIV to 12 or 24 weeks of treatment with OBV/PTV/RTV and DSV and RBV. SVR12 rates were 93.5% and 90.6% for the 12 and 24 week groups, respectively.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no data that directly or indirectly compare OBV/PTV/RTV and DSV against LDV/SOF.
- The pharmacoeconomic consequences of reinfection following treatment with OBV/PTV/RTV and DSV or other treatment regimens for CHC require further evaluation.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

May 20-21, 2015 Meeting

Regrets:

One CDEC member was unable to attend this portion of the meeting.

Conflicts of Interest:

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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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