CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

OMBITASVIR/PARITAPREVIR/RITONAVIR
(Technivie — AbbVie Corporation)
Indication: Chronic Hepatitis C Virus Genotype 4 Infection

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) be listed, in combination with ribavirin (RBV), for the treatment of adults with genotype 4 chronic hepatitis C (CHC) virus infection without cirrhosis who are either treatment-naive or were previously treated with peginterferon and ribavirin (PR), if the following conditions are met:

Conditions:
- Reduction in price to improve the cost-effectiveness to a level acceptable to the CADTH Common Drug Review (CDR)-participating drug plans
- Under the care of a physician with expertise in the diagnosis and treatment of CHC.

Reasons for the Recommendation:
1. One open-label pivotal trial (PEARL-I) demonstrated that treatment with OBV/PTV/RTV in combination with RBV was associated with high rates of sustained virologic response for 12 weeks (SVR12) in genotype 4 CHC patients without cirrhosis who were treatment-naive (100%; 95% confidence interval [CI], 91.6% to 100.0%) or PR-experienced (100%; 95% CI, 92.7% to 100.0%).
2. Based on CDR analyses, OBV/RTV/PTV is associated with an incremental cost-utility ratio (ICUR) of more than $112,000 per quality-adjusted life-year (QALY) compared with PR in treatment-naive patients, and more than $52,000 per QALY compared with no treatment in patients who are treatment-experienced; therefore, a reduction in price is required for OBV/PTV/RTV to be considered a cost-effective treatment option.

Of Note:
- Patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were excluded from the studies that CDR reviewed. CDEC noted that the use of OBV/PTV/RTV in patients coinfected with HIV and HCV provides clinical benefit in this patient population where there is an unmet therapeutic need. Because OBV/PTV/RTV contains ritonavir, it should be prescribed only in patients with suppressed HIV viral load levels. As there is also the potential for drug–drug interactions, the treatment of patients

coinfected with HIV and HCV should be under the direction of a physician experienced in managing such patients.
- CDEC noted that many patients would prefer treatment options that do not require concomitant use of RBV; however, OBV/PTV/RTV is indicated for use only in combination with RBV. In addition, non-response and relapse attributed to resistance development occurred more commonly in patients who received OBV/PTV/RTV without RBV in the included study.
- CDEC noted that the available evidence is from a small, 12-week open-label trial and is therefore inadequate to fully characterize the harms and long-term benefits associated with OBV/PTV/RTV.

Background:
Technivie is indicated in Canada for the treatment of adults with genotype 4 CHC virus infection without cirrhosis. It is a combination tablet composed of 12.5 mg OBV, 75 mg PTV, and 50 mg RTV. The recommended dosage regimen is two tablets daily of OBV/PTV/RTV in combination with RBV for 12 weeks.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials and pivotal studies of OBV/PTV/RTV, 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
Four patient groups responded to the CDR call for patient input (the Canadian Liver Foundation, the Canadian Treatment Action Group, the Pacific Hepatitis C Network, and the HepCBC Hepatitis C Education and Prevention Society). Information was gathered via online surveys (for this and from previous — but recent — reviews of HCV therapies), monthly support meetings, volunteers within some of the organizations, and a webinar that included patients diagnosed with HCV, caregivers, and health care professionals. The following is a summary of key information provided by the patient groups:
- 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, abdominal pain, muscle or joint pain, itchiness, digestive problems, depression, insomnia, nausea, diarrhea, loss of appetite, headaches, disrupted sleep, and slower motor reflexes. Cognitive functioning is affected in some patients.
- Patients must cope with the stigma associated with CHC infection and are often reluctant to disclose their HCV status for fear of rejection and discrimination.
- Patients were encouraged by the availability of this agent because of its associated frequency of SVR of between 91% and 100%, because of the limited treatment options currently available for those with genotype 4 HCV, and because it may not need to be used with interferon. However, some patients were concerned about the need for using RBV in combination with OBV/PTV/RTV because of side effects they have either experienced themselves or heard or read about.
- Some groups indicated that some patients who have a less urgent need for treatment understand they may need to wait up to a year or two for treatment, to allow those who need

treatment urgently to receive the most effective treatment available, but all groups believe strongly that all individuals with HCV — regardless of their disease severity, financial means, private or public insurance coverage, and location — have the right to prompt treatment.

Clinical Trials

The CDR systematic review included one pivotal, phase 2, open-label, uncontrolled trial. PEARL-I (N = 316, with 135 patients with genotype 4 CHC) included treatment-naive and PR-experienced genotype 4 CHC patients without cirrhosis. PEARL-I evaluated 12-week treatment with OBV/PTV/RTV with or without weight-based RBV. PEARL-I excluded patients with cirrhosis, hepatitis B, or HIV coinfection; malignancy; other significant liver disease; uncontrolled seizures; uncontrolled diabetes; or recent substance abuse.

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 the last dose of study drug.
- 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.
- Euro-QoL 5-Dimensions Questionnaire (EQ-5D) — a generic health-related quality of life instrument that may be applied to a wide range of health conditions and treatments.
- Hepatitis C Virus Patient-Reported Outcomes Instrument (HCV-PRO) has been 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’’ to ‘‘none of the time’’.

The primary outcome of PEARL-I study was the proportion of patients with SVR12.

Efficacy

- Among the patients with genotype 4 CHC infection who received OBV/PTV/RTV with or without RBV, the proportions of patients with SVR12 were:
  - 100% (95% CI, 91.6% to 100.0%) of treatment-naive patients treated with OBV/PTV/RTV + RBV
  - 100% (95% CI, 92.7% to 100.0%) of treatment-experienced patients treated with OBV/PTV/RTV + RBV
  - 90.9% (95% CI, 78.3% to 97.5%) of treatment-naive patients treated with OBV/PTV/RTV without RBV.
- No treatment-naive or treatment-experienced genotype 4 CHC patients who were treated with OBV/PTV/RTV + RBV experienced virologic failure during the treatment period or experienced a relapse during the post-treatment follow-up period. In the treatment-naive group who received OBV/PTV/RTV without RBV, one of the 44 patients experienced on-treatment virologic failure and two patients relapsed within 12 weeks post-treatment; all three patients harboured viruses with resistance-associated mutations at the time of failure that were not present at baseline.
- The mean changes from baseline in HCV-PRO scores were statistically significantly lower in the OBV/PTV/RTV + RBV group compared with the OBV/PTV/RTV without RBV groups

(indicating a poorer state of health) at the final on-treatment visit. The differences in mean changes from baseline between these two groups were not statistically significant anymore at 24 weeks post-treatment.
- There were no statistically significant differences between OBV/PTV/RTV + RBV and OBV/PTV/RTV without RBV in EQ-5D scores.

Harms (Safety and Tolerability)
- Adverse events were more commonly reported in the treatment groups that received OBV/PTV/RTV in combination with RBV than in the group that did not receive concomitant RBV (88% versus 77%). The most commonly reported adverse events were asthenia, headache, diarrhea, fatigue, insomnia, irritability, myalgia, nasopharyngitis, nausea, and pruritus.
- One treatment-naive patient in the OBV/PTV/RTV without RBV group experienced a serious adverse event. No other serious adverse events were reported in the trial.
- No patients withdrew from the study as a result of adverse events.

Cost and Cost-Effectiveness
The manufacturer submitted cost-utility analyses based upon a Markov model consisting of nine distinct health states. All patients with HCV genotype 4 infection were assumed to begin in either a mild fibrosis (METAVIR F0 to F1) or moderate fibrosis (METAVIR F2 to F3) state. Patients from either state could achieve SVR, progress from mild to moderate fibrosis, or progress to compensated cirrhosis. The model included states for decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and death. The submitted analysis allowed for reinfection, but assumed no retreatment. Decompensated cirrhosis, HCC, and liver transplant were associated with a liver-specific risk of death as well as the risk of all-cause mortality applied to all other health states. The manufacturer conducted two analyses over a patient lifetime (70 years) time horizon, from a government-payer perspective. For the analysis of treatment-naive patients eligible to receive RBV treatment, the cohort was assumed to have a mean age of 47 years at the start of the model, with 82.6% of patients in the mild fibrosis state; OBV/RTV/PTV + RBV was compared with sofosbuvir/ledipasvir (SOF/LDV), sofosbuvir + PR (SOF + PR), and PR alone. For the analysis of treatment-experienced patients, the cohort was assumed to have a mean age of 51 years, with 67.3% of patients beginning in the mild fibrosis state; only OBV/RTV/PTV + RBV and SOF/LDV were considered as comparators for this population.

Clinical effectiveness was assessed using SVR data obtained from PEARL-I for OBV/RTV/PTV + RBV from an open-label study for SOF/LDV, and from the NEUTRINO trial for SOF + PR. The manufacturer considered a range of data sources for SVR rates for PR and selected a small study (N = 13) that allowed inference of the SVR rate (76.9%) in a genotype 4 group in the mild and moderate fibrosis states (F0 to F3). Rates for five adverse events (anemia, rash, depression, neutropenia, and thrombocytopenia) were derived from a variety of clinical sources. The economic model is based on a simulated natural history derived from the large-scale meta-analysis of CHC epidemiology studies reported by Thein et al. (2008) and other sources.

The quality-of-life data attached to each health state were based on Health Utilities Index Mark 3 data from Brady et al. (2007). Short-term treatment-based EQ-5D disutilities were also calculated for each of the treatments and converted to QALY gains in the period in which treatment occurred. Costs (e.g., health state, adverse events) were based on published literature.

The manufacturer reported that OBV/RTV/PTV dominates (i.e., is less costly and more effective than) SOF/LDV for treatment-experienced patients. OBV/RTV/PTV is, however, unlikely to be cost-effective when compared with PR for patients who are treatment-naive, with an ICUR of more than $100,000 per QALY.

CDR identified the following limitations with the manufacturer's submission:

- The recent warnings regarding liver damage associated with OBV/RTV/PTV were not incorporated into the analysis, which represents an important limitation. This could not be explored in reanalyses, given the information currently available to CDR.
- The manufacturer's submission did not include a watchful waiting or no treatment comparator even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimens.
- The efficacy inputs were not stratified by fibrosis stage. It was assumed that the comparative effectiveness of SOF/LDV with other regimens is independent of fibrosis stage, which may not be an accurate reflection of the results obtained in a real-world setting.
- The results of the manufacturer's sensitivity analyses suggested that the model was highly sensitive to changes in the utility benefit assigned to achieving SVR.
- There is a lack of comparative evidence for both SVR and adverse event rates across the comparators considered.

Based on CDR analyses, OBV/RTV/PTV is associated with an ICUR of more than $112,000 per QALY when compared with PR in treatment-naive patients, and more than $52,000 per QALY compared with no treatment in treatment-experienced patients. These results do not account for the possible risk of liver damage with OBV/RTV/PTV and, as such, these estimates likely represent an underestimation of the ICURs.

The manufacturer submitted a price of $665 per daily blister (containing two tablets of OBV/RTV/PTV), corresponding to $55,860 for a 12-week treatment regimen.

Other Discussion Points:

CDEC noted the following

- For patients with genotype 4 CHC, the CADTH Therapeutic Review Report, *Drugs for Chronic Hepatitis C Infection*, suggested that the rate of SVR12 with PR for 48 weeks was 0.65 (95% credible interval [CrI], 0.63 to 0.67) in treatment-naive patients without cirrhosis and 0.61 (95% CrI, 0.50 to 0.73) for treatment-experienced patients.
- OBV/PTV/RTV is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential liver toxicity.
- Because genotype 4 CHC represents a small proportion of the overall hepatitis C patient population (e.g., 1%), the overall budget impact of OBV/PTV/RTV is likely to be small.
- OBV/PTV/RTV + RBV was not included in the CADTH Therapeutic Review Report, as it was not approved for use in Canada when the review was conducted. As part of the therapeutic review, CDEC recommended SOF + PR for 12 weeks as the preferred treatment option for genotype 4 CHC patients who are treatment-naive and do not have cirrhosis. There was insufficient evidence to make a recommendation for all other subgroups of genotype 4 CHC.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no data directly or indirectly comparing OBV/PTV/RTV against other regimens.
- The efficacy and safety of OBV/PTV/RTV have not been established in patients with cirrhosis, coinfection with HIV, coinfection with hepatitis B virus, malignancy, recent substance abuse, poor renal function, liver transplantation, or previous use of another direct-acting antiviral.
- There were relatively few patients in the included studies who had a liver fibrosis score greater than F2 at the time of enrolment.

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 Wijeysundera.

February 17, 2016 Meeting:

Regrets:
Three CDEC members were unable to attend 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 not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.