CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

OMBITASVIR/PARITAPREVIR/RITONAVIR and DASABUVIR (Holkira Pak — AbbVie Corporation) Indication: Chronic Hepatitis C Virus Genotype 1 Infection in Adults

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated June 18, 2015.

Recommendation:
CDEC recommends that ombitasvir/paritaprevir/ritonavir and dasabuvir (OMB/PAR/RIT + DAS) be reimbursed for the treatment of adults with genotype 1 chronic hepatitis C virus (CHC) infection, including those with compensated cirrhosis, if the following conditions are met:

Conditions:
- Treatment should be initiated by physicians with experience in the management of CHC patients.
- Drug plan costs for OMB/PAR/RIT + DAS should not exceed the drug plan costs of other interferon (IFN)-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 OMB/PAR/RIT + DAS achieved high rates of sustained virologic response (SVR) at 12 weeks (SVR 12) for both treatment-naive and treatment-experienced patients with genotype 1 CHC infection with or without ribavirin (RBV).
2. The pharmacoeconomic evaluation suggests that OMB/PAR/RIT + DAS leads to similar quality-adjusted life-years (QALYs) as ledipasvir/sofosbuvir (LDV/SOF). In addition, OMB/PAR/RIT + DAS is likely to be associated with an incremental cost-utility ratio (ICUR) 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 OMB/PAR/RIT + DAS according to liver fibrosis stage; however, CADTH's cost-effectiveness analysis in the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection* demonstrated that treatment of CHC is likely cost-effective

© 2016 CADTH

across all Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scores based on generally accepted thresholds. Jurisdictions will need to consider the cost impact to drug plans and overall health care system sustainability in making decisions regarding treatment eligibility.

Of Note:

- CDEC noted that the severity of liver disease in patients with CHC infection is assessed primarily by fibrosis staging using METAVIR score, and most clinicians consider a METAVIR score ≥ F2 to define more severe disease. Extrahepatic manifestations are additional considerations in defining disease severity.
- All patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of OMB/PAR/RIT + DAS with other direct-acting antiviral (DAA) regimens for CHC.
- The pharmacoeconomic consequences of reinfection following treatment with OMB/PAR/RIT + DAS or other treatment regimens for CHC require further evaluation.

Other Discussion Points:

CDEC noted the following:

- OMB/PAR/RIT + DAS 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.
- OMB/PAR/RIT + DAS 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 OMB/PAR/RIT + DAS + RBV. SVR 12 rates were 93.5% and 90.6% for the 12 and 24 week groups respectively.

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. OMB/PAR/RIT + DAS is composed of two tablets; the first is composed of 12.5 mg OMB, 75 mg PAR, and 50 mg RIT. The second tablet is composed of 250 mg DAS. The recommended dosage regimen is two tablets daily of OMB/PAR/RIT and two tablets daily of DAS, 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.

© 2016 CADTH

The product monograph recommends 24 weeks of OMB/PAR/RIT + DAS + RBV for patients with genotype 1a infection with cirrhosis, who have had a previous null response to PR.

Submission History:
In June 2015, CDEC recommended that OMB/PAR/RIT + DAS be listed for the treatment of adults with genotype 1 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 OMB/PAR/RIT + DAS should not exceed the drug plan costs of other IFN-free regimens for the treatment of CHC.

As part of a CADTH Therapeutic Review (*Drugs for Chronic Hepatitis C Infection*), CDEC issued evidence-informed recommendations in November 2015 to address the optimal use of all currently available IFN-free treatments for CHC infection for multiple genotypes.

1. All patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.
2. LDV/SOF and OMB/PAR/RIT + DAS ± RBV as preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status.
3. The following are preferred regimens for patients with CHC infection genotypes 2 through 4:
   - genotype 2: sofosbuvir (SOF)/RBV for 12 weeks
   - genotype 3 without cirrhosis: DCV/SOF for 12 weeks
   - genotype 3 with cirrhosis: SOF/RBV for 24 weeks
   - genotype 4 treatment-naive without cirrhosis: SOF + PR for 12 weeks.
4. CDEC considered there to be insufficient evidence to make a recommendation for patients with: genotype 4 CHC who are treatment-experienced or with cirrhosis regardless of treatment experience, genotype 5 CHC, and genotype 6 CHC.

The CADTH Common Drug Review (CDR)-participating jurisdictions submitted a request for advice to ask CDEC if the recommendation for OMB/PAR/RIT + DAS should be updated to align with the CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*?

Summary of CDEC Considerations:
CDEC considered the following to address the request for advice:
- Materials included in the CDEC brief for the 2015 CDR review of OMB/PAR/RIT + DAS.
- The 2015 CDEC recommendation for OMB/PAR/RIT + DAS (June 18, 2015).
- The CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*.

© 2016 CADTH

- The CDR request for advice brief, which included a detailed comparison of the key reasons and evidence underlying the CDEC recommendation for OMB/PAR/RIT + DAS and the CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*.
- Input from five patient groups which described the impacts of hepatitis C infection and expectations from therapy.

Comparison of CDEC Recommendations:
The primary difference between CDEC's recommendation from the initial CDR review of OMB/PAR/RIT + DAS and the recommendations from the therapeutic review (TR) is the presence or absence of a clinical criterion related to liver fibrosis staging. The CDEC recommendation for OMB/PAR/RIT + DAS included a clinical criterion that treatment should only be provided for patients with a liver fibrosis stage of ≥ 2. The rationale for this criterion was stated as follows: *Due to limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of OMB/PAR/RIT + DAS according to liver fibrosis stage, particularly for patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).*

In contrast to the initial CDEC recommendation for OMB/PAR/RIT + DAS, when considering the findings of CADTH's TR, CDEC recommended OMB/PAR/RIT + DAS and LDV/SOF as the preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status or fibrosis score. In the reasons for the TR recommendations, CDEC noted that CADTH's cost-effectiveness analysis demonstrated that treatment of CHC is likely cost-effective across all Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scores based on generally accepted thresholds.

Summary of Patient Input for the Current Request for Advice:
Five patient groups, the Canadian Liver Foundation, Action Hepatitis Canada, the Pacific Hepatitis C Network, the Canadian Treatment Action Council (CTAC), and the HepCBC Hepatitis C Education and Prevention Society responded to the CDR call for patient input.

- Patient groups supported that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. It was acknowledged that, should drug plans be unable to provide coverage for all patients, priority should be given to those with more severe disease.
- In general, patients are willing to tolerate treatment with ribavirin in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with ribavirin are much less severe than those associated with pegylated interferon.

Evidence from the CDR Review of OMB/PAR/RIT + DAS:

Patient Input Information
The following is a summary of information provided by five 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.

© 2016 CADTH

- 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.
- OMB/PAR/RIT+ DAS was the second therapy to become available on the market that offers an IFN-free option for CHC patients. IFN-based therapies are limited by adverse effects that can be debilitating.
- The expectations for OMB/PAR/RIT + DAS 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 OMB/PAR/RIT + DAS will open up treatment to patients who had contraindications to, or who could not tolerate, IFN-based treatments. Patients see advantages with OMB/PAR/RIT + DAS 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 IFN before becoming eligible for an IFN-free therapy. Patients believe that all those diagnosed with CHC should be able to access IFN -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-naive and treatment-experienced patients who had hepatic cirrhosis (TURQUOISE II [open-label; N = 381]). The trials evaluated 12 weeks of treatment with OMB/PAR/RIT + DAS + RBV relative to OMB/PAR/RIT + DAS alone (three trials) or OMB/PAR/RIT + DAS + 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:

- SVR 12 — 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.

© 2016 CADTH

- 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’’ to ‘‘none of the time.’’ The HCV-PRO total score is the sum of 16 individual item scores converted to a 0 to 100 scale as follows: ([sum – 16] × 100)/64. A higher HCV-PRO score indicates a better state of health.

The primary outcome of all studies was the proportion of patients with SVR 12.

Efficacy

- All OMB/PAR/RIT + DAS treatment groups demonstrated statistical superiority compared with the historical control rates for SVR 12. The proportions of patients with SVR 12 were:
  - SAPPHIRE I: 96.2% for OMB/PAR/RIT + DAS + RBV (12 weeks) versus 70% historical control rate.
  - PEARL III: 99.5% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 99% for OMB/PAR/RIT + DAS without RBV (12 weeks) versus 73% historical control rate.
  - PEARL IV: 97.0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 90.2% for OMB/PAR/RIT + DAS without ribavirin (12 weeks) versus 65% historical control rate.
  - SAPPHIRE II: 96.3% for OMB/PAR/RIT + DAS + RBV (12 weeks) versus 60% historical control rate.
  - PEARL II: 96.6% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 100% for OMB/PAR/RIT + DAS without RBV (12 weeks) versus 64% historical control rate.
  - TURQUOISE II: 91.8% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 95.9% for OMB/PAR/RIT + DAS + RBV (24 weeks) versus 43% historical control rate.
- The proportions of patients experiencing relapse were:
  - SAPPHIRE I: 1.5% for OMB/PAR/RIT + DAS + RBV (12 weeks)
  - PEARL III: 0% for both OMB/PAR/RIT +DAS ± RBV (12 weeks)
  - PEARL IV: 1% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 5.2% for OMB/PAR/RIT + DAS without RBV (12 weeks)
  - SAPPHIRE II: 2.4% for OMB/PAR/RIT + DAS + RBV (12 weeks)
  - PEARL II: 0% for both OMB/PAR/RIT + DAS ± RBV (12 weeks)
  - TURQUOISE II: 5.9% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0.6% for OMB/PAR/RIT + DAS + 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

© 2016 CADTH

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 OMB/PAR/RIT + DAS + RBV (12 weeks) and 0% for placebo.
  - PEARL III: 1.9% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 1.9% for OMB/PAR/RIT + DAS without RBV (12 weeks).
  - PEARL IV: 3.0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0.5% for OMB/PAR/RIT + DAS without RBV (12 weeks).
  - SAPPHIRE II: 2.0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 1.0% for placebo.
  - PEARL II: 2.2% for OMB/PAR/RIT + DAS and RBV (12 weeks) and 2.1% for OMB/PAR/RIT + DAS without RBV (12 weeks).
  - TURQUOISE II: 6.3% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 4.7% for OMB/PAR/RIT + DAS and RBV (24 weeks).
- The most frequent adverse events reported for the OMB/PAR/RIT + DAS regimens included fatigue (21.4% to 46.5%), headache (23.0% to 36.4%), pruritus (5.3% to 19.2%), nausea (4.3% to 23.7%), diarrhea (4.3% to 16.9%), insomnia (3.3% to 18.0%), asthenia (1% to 15.8%), rash (1% to 14.5%), and anemia (0.5% to 11%). The proportions of patients who experienced at least one adverse event were:
  - SAPPHIRE I: 87.5% for OMB/PAR/RIT +DAS + RBV (12 weeks) and 73.4% for placebo.
  - PEARL III: 80% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 67% for OMB/PAR/RIT + DAS without RBV (12 weeks).
  - PEARL IV: 92% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 82.4% for OMB/PAR/RIT + DAS without RBV (12 weeks).
  - SAPPHIRE II: 91.2% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 82.5% for placebo.
  - PEARL II: 79.1% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 77.9% for OMB/PAR/RIT +DAS without RBV (12 weeks).
  - TURQUOISE II: 91.8% for OMB/PAR/RIT +DAS + RBV (12 weeks) and 90.7% for OMB/PAR/RIT + DAS and RBV (24 weeks).
- The proportions of patients who withdrew from the trial as a result of adverse events were:
  - SAPPHIRE I: 0.6% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0.6% for placebo
  - PEARL III: 0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0% for OMB/PAR/RIT + DAS without RBV (12 weeks)
  - PEARL IV: 0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 1.0% for OMB/PAR/RIT + DAS without RBV (12 weeks)
  - SAPPHIRE II: 1.0% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0% for placebo
  - PEARL II: 2.2% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 0% for OMB/PAR/RIT + DAS without RBV (12 weeks)
  - TURQUOISE II: 1.9% for OMB/PAR/RIT + DAS + RBV (12 weeks) and 2.3% for OMB/PAR/RIT + DAS + RBV (24 weeks).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing OMB/PAR/RIT + DAS with the following: LDV/SOF; SOF + PR; telaprevir + PR; boceprevir + PR; and simeprevir + 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

© 2016 CADTH

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-naive (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 OMB/PAR/RIT + DAS 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 OMB/PAR/RIT + DAS 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 IFN-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 OMB/PAR/RIT + DAS compared with other treatment regimens. The comparative cost-effectiveness of OMB/PAR/RIT + DAS 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 OMB/PAR/RIT + DAS in all the various patient groups that are likely to seek treatment for CHC with IFN-free regimens.

At the submitted price of $665 per day, a 12-week course of OMB/PAR/RIT + DAS ($55,860) is more expensive than a 24 to 48-week course of SIM + PR (ranging from $46,002 to $55,502) and an 8-week course of LDV/SOF ($44,667), but less expensive than a 12-week course of

© 2016 CADTH

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 OMB/PAR/RIT + DAS ($111,720) 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.

Evidence from the CADTH Therapeutic Review:

Efficacy and Safety

Treatment-Naive Patients with Genotype 1 CHC

- For treatment-naive patients with genotype 1 CHC, all of the DAA treatment strategies under review, with the exception SIM/SOF for 12 weeks, significantly improved SVR compared with PR for 48 weeks (relative risk [RR] range 1.48 to 1.86). LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks significantly improved SVR compared with SOF/RBV for 24 weeks, response-guided therapy with SIM + PR, and SOF + PR for 12 weeks (result was statistically non-significant for OMB/PAR/RIT + DAS for 12 weeks versus SOF + PR for 12 weeks). There were no statistically significant differences between LDV/SOF for 12 weeks, DCV/SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks.
- Results of the subgroup analysis were consistent with those for the overall treatment-naive population, especially for the comparisons between IFN-free regimens; there were no significant differences in SVR 12 among LDV/SOF for 12 weeks, DCV/SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks where these regimens could be compared with one another.
- LDV/SOF for 12 weeks, OMB/PAR/RIT + DAS ± RBV for 12 weeks, and DCV/SOF for 12 weeks were associated with significantly lower risks for anemia than PR-based treatments, but only LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were significantly associated with less rash and depression compared with PR-based treatments. For rash, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks. There was no significant difference between DCV/SOF for 12 weeks and any of the IFN-free regimens.
- For anemia, OMB/PAR/RIT + DAS ± RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks. There was no significant difference between DCV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks or LDV/SOF for 12 weeks on this outcome.

Treatment-Experienced Patients with Genotype 1 CHC

- All of the DAA treatment strategies significantly improved SVR compared with PR (RR ranged from 2.72 to 3.75). There were no significant differences found when LDV/SOF for 12 weeks was compared with OMB/PAR/RIT + DAS ± RBV for 12 weeks. There were no trials for DCV/SOF in treatment-experienced patients.
- Results of the subgroup analyses were generally consistent with those for the overall treatment-experienced population in that no significant differences in SVR were found in most subgroups when LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were compared against each other. One exception was the subgroup analysis of patients without cirrhosis, in which OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with LDV/SOF for 12 weeks. Due to the lack of stratified baseline

© 2016 CADTH

data by prior treatment experience for OMB/PAR/RIT + DAS ± RBV for 12 weeks, this regimen was included only in the analysis of patients with cirrhosis as part of a sensitivity analysis based on certain assumptions.

- LDV/SOF for 12 weeks could not be included in any of the subgroup analyses by type of prior response — i.e., prior relapse, prior partial response, and prior null response — due to a lack of data. As well, an analysis by type of prior response was not possible for IFN-free regimens in patients with cirrhosis, due to a lack of data.
- LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments.
- For rash there was no significant difference between OMB/PAR/RIT + DAS ± RBV for 12 weeks and LDV/SOF for 12 weeks.
- For anemia, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks.

Cost-Effectiveness

CADTH conducted a cost-utility analysis of drugs for CHC infection using an updated version of the model from the 2014 CADTH Therapeutic Review of treatments for CHC infection. The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY (ICUR). Treatment effect estimates for SVR and adverse events (anemia, depression, and rash) were obtained from the CADTH systematic review and network meta-analysis. Other inputs for the economic model were derived from published sources and validated by clinical experts. Drug costs were obtained from the Ontario Drug Benefit Exceptional Access Program, Yukon Drug Formulary, the Saskatchewan Drug Plan, or directly from manufacturers.

The base-case analysis suggested that for each genotype 1 population (i.e., treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic, or treatment-experienced cirrhotic), at least one of the IFN-free therapies appeared to be economically attractive compared with PR alone (ICURs less than $30,000 per QALY). The drug that is most cost-effective varied by population, but was generally consistent across fibrosis stages.

For patients with genotype 1 CHC infection who are treatment-naive and non-cirrhotic, at a willingness to pay (λ) of $50,000 per QALY, OMB/PAR/RIT + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, LDV/SOF for 12 weeks was likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are treatment-experienced and non-cirrhotic, OMB/PAR/RIT + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone at a willingness to pay of $50,000 per QALY. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, response-guided therapy with SIM + PR was likely to be the most cost-effective option, followed by LDV/SOF + RBV for 12 weeks compared with PR alone. The incremental QALYs for OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks compared with PR were similar in all analyses.

© 2016 CADTH

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.

April 20, 2016 Meeting

Regrets:

One CDEC member was unable to participate in 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 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.

The Canadian Agency for Drugs and Technologies in Health (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.

© 2016 CADTH