# Common Drug Review
## *Request for Advice*

**May 2016**

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|---|---|
| **Drug** | ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak) |
| **Indication** | For the treatment of adults with genotype 1 chronic hepatitis C (CHC) virus infection including those with compensated cirrhosis. |
| **Manufacturer** | AbbVie Corporation |
| **Request for Advice Questions** | Should the CDEC recommendation for ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak) be updated to align with the CDEC recommendations from the CADTH Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*? |

At the time of CDR submission for Holkira Pak, the price submitted by the manufacturer to CADTH was confidential. However, the manufacturer subsequently advised that the submitted price no longer should remain confidential in the report.

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# ABBREVIATIONS

| | |
|---|---|
| **AE** | adverse event |
| **ASU** | asunaprevir |
| **BOC** | boceprevir |
| **CADTH** | Canadian Agency for Drugs and Technologies in Health |
| **CDEC** | CADTH Canadian Drug Expert Committee |
| **CDR** | CADTH Common Drug Review |
| **CHC** | chronic hepatitis C |
| **CI** | confidence interval |
| **CLDQ** | Chronic Liver Disease Questionnaire |
| **CLF** | Canadian Liver Foundation |
| **CrI** | credible interval |
| **DAA** | direct-acting antiviral |
| **DAS** | dasabuvir |
| **DCV** | daclatasvir |
| **EQ-5D** | EuroQol-5 Dimension |
| **HCV** | hepatitis C virus |
| **HCV-PRO** | hepatitis C virus patient-reported outcome instrument |
| **HIV** | human immunodeficiency virus |
| **HRQL** | health-related quality of life |
| **ICUR** | incremental cost-utility ratio |
| **LDV** | ledipasvir |
| **LLOQ** | lower limit of quantification |
| **METAVIR** | Meta-analysis of Histological Data in Viral Hepatitis |
| **NMA** | network meta-analysis |
| **NOC** | Notice of Compliance |
| **OMB** | ombitasvir |
| **PAR** | paritaprevir |
| **Peg-INF** | pegylated interferon |
| **PR** | pegylated interferon plus ribavirin |
| **QALY** | quality-adjusted life-year |
| **RBV** | ribavirin |
| **RCT** | randomized controlled trial |
| **RGT** | response guided therapy |
| **RIT** | ritonavir |
| **RNA** | ribonucleic acid |

| | |
|---|---|
| **RR** | relative risk |
| **SD** | standard deviation |
| **SF-36** | Short-Form 36 |
| **SIM** | simeprevir |
| **SOF** | sofosbuvir |
| **SVR** | sustained virologic response |
| **SVR 12** | undetectable HCV RNA levels 12 weeks after the end of treatment |
| **SVR 24** | undetectable HCV RNA levels 24 weeks after the end of treatment |
| **TEL** | telaprevir |
| **TR** | therapeutic review |

# 1. BACKGROUND

## 1.1 Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir (Holkira Pak)

Holkira Pak is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adult patients, including those with compensated cirrhosis.[1] It is a combination of ombitasvir (OMB), paritaprevir (PAR), ritonavir (RIT), and dasabuvir (DAS). Thus, OMB/PAR/RIT + DAS is composed of two tablets: the first tablet contains a fixed dose combination of 12.5 mg OMB, 75 mg PAR, and 50 mg RIT. The second tablet contains 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 ribavirin (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[1]

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 pegylated interferon and ribavirin (PR).[1]

## 1.2 CDEC Recommendation

The recommendation and reasons for the recommendation from the 2015 Canadian Drug Expert Committee (CDEC) recommendation for OMB/PAR/RIT + DAS for the treatment of adults with genotype 1 CHC infection state the following:[2]

| **Recommendation** |
|---|
| CDEC recommends 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:<br>**Clinical criterion:**<br>• Liver fibrosis stage of ≥ 2.<br>**Conditions:**<br>• Treatment should be initiated by physicians with experience in the management of CHC patients.<br>• 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. |
| **Reason(s) for 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 RBV.<br>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 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.<br>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, particularly for patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1). |

### 1.3 Conclusions from the 2015 CDR Review Reports

#### 1.3.1 CDR Clinical Review Report

The primary conclusions for the 2015 CDR *Clinical Review* report were as follows:
Six pivotal trials were included in this review. OMB/PAR/RIT + DAS administered according to the Health Canada approved regimen was associated with high rates of SVR 12 in patients with genotype 1 CHC infection, in both treatment-naive and treatment-experienced patients. These SVR 12 rates were higher than SVR 12 rates reported for the historical comparator rate derived from telaprevir + PR trials. Health-related quality of life measures showed clinically insignificant changes from baseline, and differences between treatment groups in each trial were inconsistent between the different measures.

Serious adverse events and withdrawals due to adverse events were infrequent. Characteristic adverse events associated with pegylated interferon (Peg-IFN) appeared to occur less frequently among patients treated with OMB/PAR/RIT + DAS. However, the relative efficacy and safety of OMB/PAR/RIT + DAS compared with more recent IFN-free hepatitis C virus (HCV) therapies is uncertain because of the absence of direct or indirect comparative evaluations.

#### 1.3.2 CDR Pharmacoeconomic Review Report

The primary conclusions of the *CDR Pharmacoeconomic Review* report were as follows:
A number of limitations were identified with the manufacturer's economic submission. The model structure and many of the parameters were not drawn from the best available evidence; however, these issues likely affect comparators and OMB/PAR/RIT and DAS equally. The estimates of absolute costs and QALYs should be viewed with caution. This is important if decision-makers are interested in the cost-effectiveness of IFN-free CHC therapies compared with no active treatment, a treatment option that may be chosen by patients in preference to IFN-containing regimens. For this comparison, the absolute benefit of the IFN-free regimens will drive the expected cost-effectiveness.

The evidence submitted suggests that OMB/PAR/RIT and DAS leads to similar QALYs compared with LDV/SOF. The ICUR of OMB/PAR/RIT and DAS versus LDV/SOF was sensitive to variations in drug price. As well, OMB/PAR/RIT and DAS is likely to lead to ICURs within commonly accepted thresholds versus other comparators in patients who would currently receive PR therapy, although ICURs were sensitive to variations in drug prices and were based on naive indirect comparison of efficacy and safety. As such, there is significant uncertainty regarding the comparative cost-effectiveness of OMB/PAR/RIT and DAS compared with other treatment regimens.

The submitted analyses do not provide insight into the likely cost-effectiveness of OMB/PAR/RIT and DAS in other patient groups such as community dwelling patients (e.g., patients screened for HCV in a non-clinical setting) or patients who would currently be managed with watchful waiting.

# 2. REQUEST FOR ADVICE

As part of a CADTH Therapeutic Review (TR) *Drugs for Chronic Hepatitis C Infection*,[3] CDEC issued evidence-informed recommendations[4] in November 2015 to address the optimal use of all currently available IFN-free treatments for CHC infection for multiple genotypes. These recommendations stated the following:

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: daclatasvir (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 CDR-participating jurisdictions have submitted a request for advice to inquire if the CDEC recommendations for LDV/SOF (Harvoni), SOF (Sovaldi), OMB/PAR/RIT + DAS (Holkira Pak), and DCV (Daklinza) should be updated to align with the CDEC recommendations from the TR of *Drugs for Chronic Hepatitis C Infection*?

# 3. CDR APPROACH TO THE REQUEST FOR ADVICE

To address the alignment of the CDEC recommendation from the CDR review of OMB/PAR/RIT + DAS with the CDEC recommendations from the TR of *Drugs for Chronic Hepatitis C Infection*,[4] CADTH conducted a detailed comparison of the key reasons and evidence underlying each of these recommendations.

# 4. 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 TR is the presence or absence of a clinical criterion related to liver fibrosis staging (Table 1). 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).*

**TABLE 1: CDEC RECOMMENDATIONS FOR OMB/PAR/RIT + DAS FROM THE CDR REVIEW AND HEPATITIS C THERAPEUTIC REVIEW**

| Genotype | Treatment Regimen | Recommended Patient Populations | |
|---|---|---|---|
| | | CDR Review | TR (Preferred Options) |
| 1 | OMB/PAR/RIT + DAS[a] | • PR-naive (cirrhosis)<br>• PR-naive (no cirrhosis)[b]<br>• PR-experienced (cirrhosis)<br>• PR-experienced (no cirrhosis)[b] | • PR-naive (cirrhosis)<br>• PR-naive (no cirrhosis)[c]<br>• PR-experienced (cirrhosis)<br>• PR-experienced (no cirrhosis)[c] |

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; OMB/PAR/RIT + DAS = ombitasvir, paritaprevir, ritonavir, and dasabuvir; PR=pegylated interferon plus ribavarin; TR = therapeutic review
[a] Dosing as recommended in the OMB/PAR/RIT + DAS product monograph.
[b] Restricted to patients with a liver fibrosis stage of ≥ 2.
[c] Patients with any stage of liver fibrosis.

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.

# 5. CLINICAL EVIDENCE

## 5.1 Summary of the Clinical Evidence from the CDR Review

CDEC considered the following information during their deliberations on OMB/PAR/RIT + DAS:

- A systematic review of RCTs and pivotal studies
- A critique of the manufacturer's pharmacoeconomic evaluation
- Patient group-submitted information.

### 5.1.1 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.
- 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.
- 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 is 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 unmet gap in patient needs. Although it requires a slightly more complex daily regimen than LDV/SOF, the length of treatment with OMB/PAR/RIT + DAS is 12 weeks and is 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 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.

### 5.1.2 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 (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. 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 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.
- 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 (HRQL). SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional challenges. SF-36 also provides two component summaries, the physical component summary and the mental component summary.
- EuroQol 5-Dimensions (EQ-5D) Questionnaire—a generic HRQL 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 on 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.

### 5.1.3 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 RBV (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 clinically meaningful changes occurred during treatment, there was also no substantive deterioration in HRQL scores during treatment.

### 5.1.4 Harms

- 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 + 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 + RBV (24 weeks).
- The most frequently reported adverse events with OMB/PAR/RIT + DAS 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 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 + 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).

## 5.2 Summary of the Clinical Evidence from the Therapeutic Review

CDEC considered the results of CADTH's systematic review and network meta-analysis (NMA) of published literature on interventions of interest for the treatment of CHC infection. The review was an update to the 2014 CADTH TR on direct-acting antivirals (DAAs) for CHC genotype 1 infection, and also extended the scope to genotypes 2 through 6. Regimens were included if approved for use in Canada or recommended in major Canadian or US guidelines, even if not approved. A number of emerging regimens were also included in the analysis. As most newer regimens have been approved on the basis of uncontrolled or historically controlled studies, such trial designs were included in the review.

The review included 67 new publications describing 63 unique studies, in addition to 10 studies from the previous TR. In genotype 1, there were 35 studies for treatment-naive patients (additional five studies for emerging treatments), and 26 studies for treatment-experienced patients (additional two studies for emerging treatments).

The main efficacy outcome of interest was SVR at 12 weeks (SVR 12) or 24 weeks. Key safety outcomes were rash, depression, and anemia.

Bayesian NMAs were conducted for SVR 12 and key safety outcomes (i.e., rash, anemia, and depression) for both treatment-naive and treatment-experienced patients. Single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm. SVR was also analyzed according to cirrhosis status within treatment-naive and -experienced patients, and a number of subgroup analyses were performed. Treatment-experienced patients were further analyzed based on their response to prior treatment; i.e., whether they experienced relapse, partial response, or null response. The review also assessed the available evidence for patients previously treated with DAA-based regimens.

### 5.2.1 Genotype 1

#### a) Treatment-Naive

The evidence network for SVR 12 in treatment-naive genotype 1 patients included 35 studies and a total of 6,766 participants. All of the DAA treatment strategies under review, except simeprevir (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 (RGT) 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. Due to the lack of stratified baseline data by prior treatment experience for OMB/PAR/RIT + DAS ± RBV for 12 weeks, this regimen was included only for patients with cirrhosis, and patients with HIV co-infection, as part of sensitivity analyses based on certain assumptions. There were no data for DCV/SOF specific to patients with genotype 1a or genotype 1b infection, and no trials for this regimen in patients with cirrhosis or HIV co-infection.

Table 2 summarizes selected subgroup results for SVR in treatment-naive patients with genotype 1 infection.

**TABLE 2: SUMMARY OF SELECTED SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-NAIVE PATIENTS WITH GENOTYPE 1 INFECTION**

| Subgroup | Studies (N) | Main Findings |
|---|---|---|
| Genotype 1a | 18 (3,594) | No significant differences between LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS + RBV for 12 weeks. |
| Genotype 1b | 20 (2,379) | No significant differences between LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks. |
| Patients with cirrhosis | 14 (539) | No significant differences between OMB/PAR/RIT + DAS + RBV for 12 weeks, LDV/SOF ± RBV for 12 weeks, and SOF + PR for 12 weeks. |
| Patients without cirrhosis | 29 (6,018) | No significant differences between SOF 8 + LDV 8, LDV/SOF for 12 weeks, DCV/SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks. |
| HIV co-infection | 6 (410) | No significant difference between LDV/SOF for 12 weeks and SOF/RBV for 24 weeks. Also no significant differences between these regimens and OMB/PAR/RIT + DAS + RBV for 12 weeks. |

DAS = dasabuvir; DCV = daclatasvir; HIV = human immunodeficiency virus; LDV = ledipasvir; LDV 8 = ledipasvir for 8 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RIT = ritonavir; SOF = sofosbuvir; SOF 8 = sofosbuvir for 8 weeks.

#### b) Treatment-Experienced

This analysis included 26 studies and a total of 4,146 participants. Compared with PR for 48 weeks, all of the DAA treatment strategies significantly improved SVR (RR ranged from 2.72 to 3.75). No significant differences were 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 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, analysis by type of prior response was not possible for IFN-free regimens in patients with cirrhosis, due to a lack of data.

Table 3 presents selected results for the subgroup analysis of SVR for treatment-experienced patients with genotype 1 infection.

**TABLE 3: SELECTED SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-EXPERIENCED PATIENTS WITH GENOTYPE 1 INFECTION**

| Subgroup | Studies (N) | Main Findings |
|---|---|---|
| Genotype 1a | 12 (1,683) | No significant differences between LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS + RBV for 12 weeks. |
| Genotype 1b | 17 (2,135) | OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with LDV/SOF for 12 weeks. However, the same regimen without RBV did not significantly improve SVR. |
| Patients with cirrhosis | 14 (850) | No significant differences between OMB/PAR/RIT + DAS + RBV for 12 weeks, LDV/SOF ± RBV for 12 weeks, SOF 24 + LDV 24, SIM/SOF for 12 weeks, or SOF 12 PR 12. |
| Patients without cirrhosis | 19 (3,038) | OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with LDV/SOF for 12 weeks. |
| HIV co-infection | 1 (21) | OMB/PAR/RIT + DAS + RBV for 12 or 24 weeks demonstrated high SVR rates. |
| Treatment-experienced with prior relapse | 7 (741) | No significant difference between OMB/PAR/RIT ± RBV for 12 weeks and LDV/SOF for 12 weeks. |
| Treatment-experienced with prior partial response | 10 (840) | OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with SIM 12 + PR for 48 weeks.<br>No significant difference between OMB/PAR/RIT + DAS for 12 weeks, OMB/PAR/RIT + DAS + RBV for 12 weeks or SIM/PR 12/48 weeks. |
| Treatment-experienced with prior null response | 17 (1,403) | OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with SOF + PR for 12 weeks and SIM/PR 12/48 weeks.<br><br>No significant difference between OMB/PAR/RIT + DAS for 12 weeks and OMB/PAR/RIT + DAS + RBV for 12 weeks or SIM/PR 12/48 weeks. |
| Genotype 1a, treatment-experienced with prior null response | 5 (478) | Both OMB/PAR/RIT + DAS + RBV for 12 weeks and OMB/PAR/RIT + DAS + RBV for 24 weeks significantly improved SVR compared with SIM/PR 12/48 weeks. |

DAS = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LDV 24 = ledipasvir for 24 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; PR 12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; RIT = ritonavir; SIM = simeprevir; SIM12 = simeprevir for 12 weeks; SOF = sofosbuvir; SOF8 = sofosbuvir for 8 weeks; SOF 12 = sofosbuvir for 12 weeks; SOF 24 = sofosbuvir for 24 weeks; SVR = sustained virologic response.

**c) Safety**

Safety outcomes were assessed across genotypes, but separately for treatment-naive and treatment-experienced patients. Among treatment-naive patients, 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, and OMB/PAR/RIT + DAS 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. For depression, OMB/PAR/RIT + DAS + RBV for 12 weeks and DCV/SOF for 12 weeks were less favourable than LDV/SOF for 12 weeks. The result for OMB/PAR/RIT + DAS + RBV should be considered in context of the patient population enrolled in the only study contributing data for this outcome, which consisted of injection drug users on stable methadone treatment that was likely at higher risk for comorbid depression compared with the broader population of patients with CHC infection.

For treatment-experienced patients, 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. Evidence was limited for depression in treatment-experienced patients. There was insufficient evidence to include DCV/SOF in the analyses of these adverse events for treatment-experienced patients.

# 6. COST EVIDENCE

## 6.1 Summary of the Pharmacoeconomic Evidence from the CDR Review of OMB/PAR/RIT + DAS

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

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 remained 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. The results were also 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 and 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 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 OMB/PAR/RIT and 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.

## 6.2 Summary of the Pharmacoeconomic Evidence from the Therapeutic Review

The follow section provides a brief summary of CADTH's pharmacoeconomic evaluation from the TR, focused on the results for patients with genotype 1 CHC. For complete details and results see the following CADTH report: *Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis*.[5]

### 6.2.1 Methods

The cost-utility analysis of drugs for CHC infection was performed using an updated version of the model used for the 2014 CADTH TR of treatments for CHC infection.[6] The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY. Of the treatment regimens that met the inclusion criteria of the protocol for the clinical review, only those treatments with price information available at the time of analysis were included in the base-case cost-utility analysis. DCV and asunaprevir (ASU) were included in exploratory analyses as they had been submitted to CDR at the time of analysis, but there were no publicly available prices for these drugs. Various price scenarios were therefore modelled and are presented in the draft cost-effectiveness report posted for stakeholder consultation. However, since posting of this report, the manufacturer has provided the list price for DCV and the analyses were re-run using this price for CDEC deliberation. During the course of the TR, the CDR review of ASU was suspended and the drug had not yet been approved by Health Canada. As a result, cost-effectiveness results for ASU were not considered by CDEC in developing recommendations.

Treatment effect estimates for SVR and adverse events (anemia, depression, and rash) were obtained from the CADTH systematic review and NMA. 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. Extensive sensitivity analyses were conducted to test the effect of changes in underlying parameter values (parameter uncertainty) and assumptions within the models (structural uncertainty).

### 6.2.2 Genotype 1

The results of the base-case analysis suggest that for each genotype 1 population (treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic, or treatment-experienced cirrhotic), at least one of the IFN-free therapies appears 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, RGT 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.

A number of exploratory analyses were conducted for genotype 1 patients to reflect key sensitivity analyses performed as part of the NMAs for this population, as well as to account for DCV/SOF for 12 weeks, for which a publicly listed price was not available at the time of the original analysis:

- When including LDV/SOF for eight weeks in the analysis of patients who are treatment-naive without cirrhosis, this regimen was the most cost-effective option (ICUR $17,287 per QALY).

- When OMB/PAR/RIT + DAS + RBV for 12 weeks was included for patients with cirrhosis, it was the most cost-effective option for both treatment-naive and treatment-experienced patients (ICUR $23,047 per QALY).
- When DCV/SOF for 12 weeks was considered for treatment-naive patients without cirrhosis, it was dominated by both OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks; however, the incremental QALYs when compared with PR were similar for all three regimens.

# 7. CONCLUSIONS

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. In contrast, the CDEC recommendation for genotype 1 CHC, indicated that OMB/PAR/RIT + DAS is a preferred regimen for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status or fibrosis score. The difference between the CDEC recommendation from the CDR review of OMB/PAR/RIT + DAS and the CDEC recommendations following the TR is attributed to CADTH's cost-effectiveness analysis, which demonstrated that treatment of CHC is likely cost-effective across all METAVIR scores based on generally accepted thresholds. Therefore, CDEC concluded that CADTH's analysis addressed the uncertainty regarding whether or not treatment with OMB/PAR/RIT + DAS is cost-effective in patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).

# APPENDIX 1: PATIENT GROUP INPUT

*This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed.*

As part of this request for advice process, the CADTH review team and CDEC consider all patient input that was received during the CDR reviews for the individual drugs and the TR of hepatitis C drugs. In addition, CADTH contacted the patient groups who provided input in the individual CDR reviews and/or TR, and invited them to provide information on the following:

- *Is there anything the CADTH review team and CDEC should be aware or reminded of, if updating individual recommendations for Harvoni, Holkira Pak, Sovaldi, and/or Daklinza?*
- *How do patients feel about hepatitis C treatments that require concomitant administration of ribavirin?*

In response to the targeted call for patient input, CADTH received responses from the following five patient groups: The Canadian Liver Foundation (CLF), HepCBC Hepatitis C Education and Prevention Society, Action Hepatitis Canada, the Canadian Treatment Action Council, and the Pacific Hepatitis C Network.

In general, all patient groups indicated that they support the alignment of the CDEC recommendations from the individual CDR reviews with the recommendations from the recent CADTH TR. A summary of key information is provided below.

**Fibrosis Stage**

All patient groups support CDEC's recommendation from the TR that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. It was noted that providing earlier access to treatment can reduce the emotional, physical, and mental strain on patients and their support communities. Patient groups also suggested that healthier patients have a greater probability of successfully responding to treatment and that such patients may be at a lower risk of experiencing toxicities due to treatment (e.g., liver damage).

The CLF also noted that there are significant practical challenges with using a liver fibrosis stage of 2 as the threshold for reimbursing treatment for CHC. They noted that the currently available diagnostic modalities lack the precision to accurately identify stage 2 liver fibrosis in all patients. This can lead to situations where patients with a fibrosis stage of 2 are misdiagnosed as having a lower stage and, therefore, are mistakenly considered to be ineligible for treatment with a DAA.

**Ribavirin**

In the various patient input submissions received during the individual CDR reviews and the TR, CADTH and CDEC identified some differences of opinion from patient groups regarding the tolerability of treatment regimens containing ribavirin (RBV). As result, CADTH included a specific question in the call for patient input asking patient groups to provide clarity on how patients perceive the benefits and harms associated with RBV.

Patient groups indicated that, in general, patients are willing to tolerate treatment with RBV in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with RBV are much less severe than those associated with pegylated interferon. It was noted that it could be beneficial for patients who may be reluctant to initiate a RBV-containing treatment regimen to receive counselling from health care providers regarding the severity and duration of adverse effects. It was suggested that this could potentially address confusion and misconceptions regarding the relative adverse effects of ribavirin compared with pegylated interferon.

**Cost and Prioritization of Treatment**

One patient group expressed concern regarding the high cost of hepatitis C treatments and the financial burden they place on public drug plans. They suggested that, although the treatments may be cost-effective, CDEC should encourage drug plans to seek reductions in price to help limit the difficulties in providing coverage for such high cost treatments. 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.

**Genotypes 4, 5, 6 and Mixed-Genotypes**

The CLF noted that CDEC has not issued recommendations about the treatment of genotypes other than 1, 2 and 3. They noted that publicly available data suggest that all-oral regimens achieve high rates of SVR for patients with genotypes 4, 5, or 6 and that patients should have access to these treatments. It was suggested that the CDEC recommendations should follow the recommendations of the *Canadian Association for the Study of the Liver (CASL) Consensus Guidelines* for the treatment of these genotypes.[7]

The CLF also noted that there is an unmet need for patients who are infected with more than one genotype of the hepatitis C virus, as some provinces are not reimbursing treatment for mixed genotypes. Although infection with multiple hepatitis C viral genotypes is a relatively rare occurrence, without reimbursement there are no funded treatment options for these patients. The CLF suggested that CADTH should help address this issue by noting that the rarity of this occurrence means there is unlikely to be clinical evidence in this population and that as long as the antivirals that are prescribed adequately cover both genotypes, the response rates are likely to be no different than for mono-infected.

**Extra-Hepatic Disease**

The CLF noted that CADTH has not issued any recommendations to fund treatment for a patient with significant extra-hepatic manifestation of CHC. It was noted that there is inconsistency across jurisdictions, with some providing coverage for these patients through various exceptional access mechanisms and others not providing any coverage. The CLF noted that there are very few of these patients, so the financial implications could be relatively small, but the clinical impact would be significant.

# APPENDIX 2: COST TABLES

| Drug | Strength | Dosage Form | Price ($) | Recommended Dose | Duration | Cost For 1 Course of Therapy ($) | Cost for 1 Course of Regimen ($) |
|---|---|---|---|---|---|---|---|
| **IFN-Free Regimens** | | | | | | | |
| OMB/PAR/RIT + DAS (Holkira Pak) | 12.5/75/50 mg<br><br>250 mg | Tablet | $665.00 | 2 X 12.5/75/50 mg OMB/PAR/RIT once daily and DAS 250 mg twice daily | 12 weeks[a] | 55,860 | 55,860 |
| OMB/PAR/RIT + DAS (Holkira Pak) + RBV | 12.5/75/50 mg 250 mg | Tablet | $665.00 | As above | 12 to 24 weeks[a] | 55,860 to 111,720 | 58,905 to 119,028 |
| | 400 mg<br>600 mg | | 14.50<br>21.75 | plus 1,000 mg to 1,200 mg/day RBV | | 3,045 to 7,308 | |
| LDV/SOF (Harvoni) | 90/400 mg | Tablet | 797.62[b] | 90 mg/400 mg once daily | 8 to 24 weeks[c] | 8 weeks: 44,667<br>12 to 24 weeks: 67,000 to 134,000 | 44,667<br>67,000 to 134,000 |
| DCV (Daklinza)/ SOF (Sovaldi) ± RBV | 60 mg | Tablet | 428.57[d] | 60 mg once daily | 12 or 24 weeks | 36,000[d] | 91,000 to 138,000<br><br>24 weeks with RBV 142,872 |
| | 400 mg | Tablet | 654.76 | 400 mg once daily | | 55,000 to 110,000 | |
| | 400 mg<br>600 mg | Tablet | 14.50<br>21.75 | 800 mg daily | 24 weeks | 4,872 | |
| SIM (Galexos) + SOF (Sovaldi) | 150 mg | Caplet | 434.55 | 150 mg once daily | 12 to 24[e] weeks | 36,502 to 73,004 | 91,502 to 183,004 |
| | 400 mg | Tablet | 654.76 | 400 mg once daily | | 55,000 to 110,000 | |
| **DAAs in Combination With PR Therapy** | | | | | | | |
| SOF (Sovaldi) + PR | 400 mg | Tablet | 654.76 | 400 mg once daily | 12 weeks[f] | 55,000 | 59,750 |
| | 180 mcg/200 mg | Vial/tablets | 395.84 | Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day[g] | 12 weeks | 4,750 | |
| SOF (Sovaldi)/RBV | 400 mg | Tablet | 654.76 | 400 mg once daily | 24 weeks | 110,000 | 116,090 to 117,308 |
| | 400 mg<br>600 mg | Tablet | 14.50[b]<br>21.75[b] | 1,000 mg to 1,200 mg daily | 24 weeks | 6,090 to 7,308 | |
| SIM (Galexos) + PR | 150 mg | Caplet | 434.55 | 150 mg once daily | 12 weeks | 36,502 | 46,002 to 55,502 |
| | 180 mcg/200 mg | Vial/tablets | 395.84[g] | Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day | 24 to 48 weeks | 9,500 to 19,000 | |
| BOC (Victrelis) + PR | 200 mg | Caplet | 12.50 | 4 x 200 mg 3 times daily | 24 to 44 weeks | 25,200 to 46,200 | 37,365 to 67,055 |
| | 120 mcg/200 mg | Pens/caplets | 868.96 | Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day | 28 to 48 weeks | 12,165 to 20,855 | |

| Drug | Strength | Dosage Form | Price ($) | Recommended Dose | Duration | Cost For 1 Course of Therapy ($) | Cost for 1 Course of Regimen ($) |
|---|---|---|---|---|---|---|---|
| **PR Therapy** | | | | | | | |
| Peg-IFN alfa-2a + RBV (Pegasys RBV) | 180 mcg /200 mg | Vial or syringe<br>28 tablets<br>35 tablets<br>42 tablets | 395.84 | Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day[c] | 24 to 48 weeks | 9,500 to 19,000 | 9,500 to 19,000 |
| Peg-IFN alfa-2b + RBV (Pegetron) | 50 mcg/200 mg | 2 vials + 56 caplets | 786.39 | Peg-IFN 1.5 mcg/kg/week; RBV 800 mg 1,400 mg/day[c] | 24 to 48 weeks | 9,437 to 18,873 | 9,437 to 18,873 |
| | 150 mcg/200 mg | 2 vials + 84 or 98 caplets | 868.96 | | | 10,428 to 20,855 | 10,428 to 20,855 |
| | 80 mcg/200 mg<br>100 mcg/200 mg<br>120 mcg/200 mg<br>150 mcg/200 mg | 2 pens/56 to 98 caplets | 786.39<br>786.39<br>868.96<br>868.96 | | | 9,437 to 20,855 | 9,437 to 20,855 |
| TEL (Incivek) + PR | 375 mg | Tablet | 69.38 | 3 x 375 mg two times daily | 12 weeks | 34,968 | 44,468 to 53,968 |
| | 180 mcg /200 mg | Vial/tablets | 395.84 | Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day[h] | 24 to 48 weeks | 9,500 to 19,000 | |
| BOC + PR (Victrelis Triple) | 200/80/200<br>200/100/200<br>200/120/200<br>200/150/200<br>(mg/mcg/mg) | 168 caplets +<br>2 pens +<br>56 caplets | 2652.55[g]<br>2652.55[g]<br>2726.00[g]<br>2726.00[g] | BOC 800 mg 3 times daily; peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg per day | 24 to 44 weeks | 31,831 to 59,972 | 31,831 to 59,972 |

BOC = boceprevir; DAS = dasabuvir; DCV = daclatasvir; IFN = interferon; IM = intramuscular; IU = international unit; IV = intravenous; LDV = ledipasvir; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RIT = ritonavir; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.

[a] 12 weeks of PAR/RIT /OMB + DAS alone for patients with genotype 1b without cirrhosis; 12 weeks of PAR/RIT/OMB + DAS plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks PAR/RIT /OMB + DAS plus RBV for patients with genotype 1a with cirrhosis who had previous null response to PR. Price obtained from AbbVie website.[8]

[b] Yukon Drug Formulary (March 2015)[9] and Ontario Exceptional Access Program (March 24, 2015).[10]

[c] 12 weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. 8 weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment hepatitis C virus RNA less than 6 million IU/mL.

[d] Provided by Bristol-Myers Squibb Canada Inc.

[e] Treatment for up to 24 weeks' duration should be considered in patients with cirrhosis.

[f] 12 weeks for genotype 1, 2, 4; 16 to 24 weeks for genotype 3.

[g] Ontario Drug Benefit Formulary (March 2015).[11]

[h] Dosing varies by weight and HCV genotype.

Source: Saskatchewan Drug Benefit (February 2015) prices unless otherwise stated.[12]

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