Common Drug Review
Request for Advice

May 2016

Drug	ledipasvir/sofosbuvir (Harvoni)
Indication	For the treatment of chronic hepatitis C (CHC) virus genotype 1 infection in adults.
Manufacturer	Gilead Sciences Canada, Inc.
Request for Advice Questions	Should the CDEC recommendation for ledipasvir/sofosbuvir (Harvoni) be updated to align with the CDEC recommendations from the CADTH Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*?

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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
FACIT-F	Functional Assessment of Chronic Therapy - Fatigue
HCV	hepatitis C virus
HIV	human immunodeficiency virus
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

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
TR	therapeutic review
WPAI	Work Productivity and Activity Impairment Questionnaire

1. BACKGROUND

1.1 Ledipasvir/Sofosbuvir (Harvoni)

Ledipasvir/sofosbuvir (LDV/SOF) is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.[1] LDV/SOF is available as a single fixed-dose tablet containing 90 mg LDV and 400 mg SOF. It is administered orally once daily for 8 to 24 weeks, with duration determined by prior treatment experience and the presence of cirrhosis:

- 12 weeks for treatment-naive genotype 1 patients with or without cirrhosis and treatment-experienced patients without cirrhosis.
- 24 weeks for treatment-experienced genotype 1 patients with cirrhosis.
- A duration of eight weeks for treatment-naive patients can be considered if the pre-treatment hepatitis C virus (HCV) viral load is less than 6 million IU/mL.[1]

1.2 CDEC Recommendation

The recommendation and reasons for the recommendation from the 2015 CDEC recommendation for LDV/SOF for the treatment of CHC genotype 1 infection in adults states the following:[2]

Recommendation
CDEC recommends that LDV/SOF be listed for the treatment of CHC genotype 1 infection in adults, if the following clinical criterion and conditions are met: **Clinical criterion:** • Liver fibrosis stage ≥ 2 **Conditions:** • Treatment should be initiated by physicians with experience in the management of patients with CHC infection. • Substantial reduction in price
Reason(s) for Recommendation
1. Three randomized controlled trials (RCTs) (ION-1, ION-2, and ION-3) demonstrated that treatment with LDV/SOF with or without ribavirin (RBV) 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. 2. At the submitted price ([redacted] per tablet containing 90 mg LDV and 400 mg SOF), LDV/SOF is considered to be a cost-effective treatment option compared with SOF or simeprevir (SIM) in combination with pegylated interferon and ribavirin (PR) for treatment-naive patients and treatment-experienced patients without cirrhosis. 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 insufficient clinical evidence and limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of LDV/SOF 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 Common Drug Review (CDR) Reports

1.3.1 CDR Clinical Review Report

The primary conclusions of the 2015 *CDR Clinical Review* were as follows:[3]

LDV/SOF administered for the Health Canada-approved durations was associated with high rates of SVR 12 in patients with genotype 1 CHC infection, in both treatment-naive and treatment-experienced patients. These rates were statistically significantly higher than historical control rates for direct-acting antiviral (DAA)-containing regimens. The addition of ribavirin (RBV) to LDV/SOF did not appear to improve SVR 12 rates. LDV/SOF appeared to be better tolerated in a number of respects compared to RBV-containing regimens in the three pivotal trials. There were no direct comparative trials of LDV/SOF against existing DAA-containing regimens. The manufacturer-submitted network meta-analysis (NMA)

showed higher SVR rates with LDV/SOF than PR-based DAA regimens; however, significant methodological limitations were noted that reduce confidence in the reported effect estimates. This renders it difficult to estimate the incremental benefit on SVR of LDV/SOF compared with other regimens. Health-related quality of life scales demonstrated mixed and marginal changes from baseline to end of therapy. Relapse rates were low throughout all the trials, although the trials have limited long-term follow-up. Although some of the characteristic adverse effects associated with pegylated interferon (Peg-IFN) and RBV appeared to occur less frequently among patients treated with LDV/SOF, the lack of comparative data against existing regimens for CHC infection makes it difficult to judge the relative safety profile of LDV/SOF.

1.3.2 CDR Pharmacoeconomic Review Report

The primary conclusions of the *CDR Pharmacoeconomic Review* report were as follows:
Given the high SVR rates observed with LDV/SOF, it is not surprising that in non-cirrhotic patients, CDR reanalyses find it is still likely to be cost-effective. Intuitively, it is unlikely that a *de novo* model that resolved the many faults with the submitted analysis would arrive at a different conclusion. Nonetheless, CDR considers that these results are likely to be an underestimate of the actual incremental cost-utility ratios (ICUR) of LDV/SOF versus other comparators.

In treatment-experienced cirrhotic patients, ICURs of LDV/SOF versus SOF + PR were consistently greater than $50,000 per quality-adjusted life-year (QALY), with the probability of the ICUR being less than $50,000 per QALY at less than 30%. The ICUR of LDV/SOF versus simeprevir (SIM) + PR went up to $36,000 per QALY. The estimates of the cost-effectiveness of LDV/SOF in cirrhotic treatment-experienced patients are similarly limited by the flaws in the submitted model, and even CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

2. REQUEST FOR ADVICE

As part of a CADTH Therapeutic Review (TR) *Drugs for Chronic Hepatitis C Infection*[4], CDEC issued evidence-informed recommendations[5] in November 2015 to address the optimal use of all currently available interferon (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 ombitasvir/paritaprevir/ritonavir + dasabuvir (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: 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 the following: genotype 4 CHC who are treatment-experienced or with cirrhosis regardless of treatment, 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 LDV/SOF[2] with the CDEC recommendations from the TR of *Drugs for Chronic Hepatitis C Infection*,[5] 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 individual review of LDV/SOF 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 LDV/SOF 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 insufficient clinical evidence and limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of LDV/SOF 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 LDV/SOF FROM THE CADTH CDR REVIEW AND HEPATITIS C THERAPEUTIC REVIEW

Genotype	Treatment Regimen	Recommended Patient Populations	
		CDR Review	TR (Preferred Options)
1	LDV/SOF[a]	• PR-naive (cirrhosis) • PR-naive (no cirrhosis)[b] • PR-experienced (cirrhosis) • PR-experienced (no cirrhosis)[b]	• PR-naive (cirrhosis) • PR-naive (no cirrhosis)[c] • PR-experienced (cirrhosis) • PR-experienced (no cirrhosis)[c]

CADTH = Canadian Agency for Drugs and Therapeutics in Health; CDEC = Canadian Drug Expert Committee; CDR = Common Drug Review; LDV = ledipasvir; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir

[a] Dosing as recommended in the LDV/SOF 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 LDV/SOF, when considering the findings of CADTH's TR, CDEC recommended LDV/SOF and OMB/PAR/RIT + DAS ± RBV 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 of LDV/SOF

CDEC considered the following information during their deliberations on LDV/SOF:

- A systematic review of RCTs and pivotal studies.[3]
- A critique of the manufacturer's pharmacoeconomic evaluation.[6]
- Patient group-submitted information.

5.1.1 Patient Input Information

The following is a summary of information provided by six 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.
- Current therapy is limited by adverse effects that can be debilitating. In addition, some treatment regimens may require patients to take up to 20 pills throughout the day.
- The expectations for LDV/SOF are that it will address a large unmet gap in patient needs. There is currently no treatment available for patients with a null response or relapse to standard therapies. Due to its low toxicity and lack of drug interactions, it is expected that LDV/SOF will open up treatment to patients who had contraindications to, or who could not tolerate, INF-based treatments. Patients see advantages with LDV/SOF that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients, higher response rates.

5.1.2 Clinical Trials

The CDR systematic review included three pivotal phase 3 RCTs (ION-1, ION-2, and ION-3). All trials were multi-group open-label RCTs designed to assess various durations of LDV/SOF 90 mg/400 mg with or without RBV in patients with genotype 1 CHC infection. ION-1 (N = 870) was a four-group open-label trial in treatment-naive patients: LDV/SOF for 12 weeks, with or without RBV, and LDV/SOF for 24 weeks, with or without RBV. ION-3 (N = 647) was a three-group trial that assessed LDV/SOF for eight weeks, with or without RBV, and LDV/SOF for 12 weeks, in treatment-naive patients with CHC genotype 1 infection. ION-2 (N = 441) had the same treatment groups as ION-1, but enrolled treatment-experienced patients with CHC genotype 1 infection who had had either a relapse or non-response to an IFN-based regimen (including regimens containing NS3/4A protease inhibitors). ION-1 and ION-2 both allowed enrolment of up to 20% of the patients with confirmed cirrhosis, while ION-3 excluded patients with 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 and human immunodeficiency virus (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.
- 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. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical and emotional challenges. SF-36 also provides two component summaries, the physical component summary and the mental component summary.
- Chronic Liver Disease Questionnaire (CLDQ)—an instrument used to assess the health-related quality of life for patients with chronic liver disease. CLDQ measures activity/energy, emotion, worry, and systemic symptoms, which are combined in the CLDQ total score. All domains and the total score are based on a Likert scale of 0 (worst) to 7 (best).
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale—a 40-item scale used to assess fatigue and the impact of fatigue on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale, make up the total score ranging from 0 (worst) to 160 (best).
- Work Productivity and Activity Impairment (WPAI) questionnaire—an instrument used to measure the impact of a disease on work and on daily activities.

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

5.1.3 Efficacy

- All treatment groups were statistically significantly superior to the historical control rates for SVR 12 ($P < 0.001$). The proportion of patients with SVR 12 was reported as follows:
  - ION-1: 99% for LDV/SOF (12 weeks), 97% for LDV/SOF + RBV (12 weeks), 98% for LDV/SOF (24 weeks), and 99% for LDV/SOF + RBV (24 weeks) versus the 60% historical control rate.
  - ION-2: 93.6% for LDV/SOF (12 weeks), 96.4% for LDV/SOF + RBV (12 weeks), 99.1% for LDV/SOF (24 weeks), and 99.1% for LDV/SOF + RBV (24 weeks) versus the 25% historical control rate.
  - ION-3: 94% for LDV/SOF (eight weeks), 93.1% for LDV/SOF + RBV (eight weeks), and 95.4% for LDV/SOF (12 weeks) versus the 60% historical control rate.
    - As a secondary analysis, both LDV/SOF and LDV/SOF + RBV for eight weeks were non-inferior to LDV/SOF for 12 weeks (based on a non-inferiority margin of 12%).
- The proportion of patients experiencing relapse was reported as follows:
  - ION-1: 0.5% in both the LDV/SOF (12 weeks) and LDV/SOF (24 weeks) groups.
  - ION-2: 6.5% for LDV/SOF (12 weeks), 3.6% for LDV/SOF + RBV (12 weeks), 0% in both of the 24-week treatment groups.
  - ION-3: 5.1% for LDV/SOF (8 weeks), 4.2% for LDV/SOF + RBV (8 weeks) and 1.4% for LDV/SOF (12 weeks).
- Changes in SF-36, CLDQ-HCV, and FACIT-F scores from baseline to the end of treatment were modest and typically showed improvement from baseline; however, there were no comparisons made between treatment groups.

5.1.4 Harms

- The most common adverse events reported for LDV/SOF regimens included fatigue, headache, and nausea (all > 10%). When RBV was combined with LDV/SOF, the regimen was associated with higher rates of cough, pruritus, rash, insomnia, irritability, and anemia than those that did not contain RBV.
- The proportion of patients who experienced at least one adverse event was reported as follows:
  - ION-1: 78.5% for LDV/SOF (12 weeks), 84.8% for LDV/SOF + RBV (12 weeks), 81.6% for LDV/SOF (24 weeks), and 92.2% for LDV/SOF + RBV (24 weeks).
  - ION-2: 67% for LDV/SOF (12 weeks), 86.5% for LDV/SOF + RBV (12 weeks), 80.7% for LDV/SOF (24 weeks), and 90.1% for LDV/SOF + RBV (24 weeks).
  - ION-3: 67.4% for SOF/LDV (8 weeks), 76.4% for LDV/SOF + RBV (8 weeks), and 69% for SOF/LDV (12 weeks).
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - ION-1: 0.5% for LDV/SOF (12 weeks), 3.2% for LDV/SOF + RBV (12 weeks), 8.3% for LDV/SOF (24 weeks), and 2.8% for LDV/SOF + RBV (24 weeks).
  - ION-2: 0.0% (no patients) in the 12-week treatment groups, 5.5% for LDV/SOF (24 weeks), and 2.7% for LDV/SOF + RBV (24 weeks).
  - ION-3: 1.9% for LDV/SOF (8 weeks), 0.5% for LDV/SOF + RBV (8 weeks), and 2.3% for LDV/SOF (12 weeks).
- The proportion of patients who experienced an adverse event leading to discontinuation of any study drug was reported as follows:
  - ION-1: 0% for LDV/SOF (12 weeks), 0.5% for LDV/SOF/RBV (12 weeks), 1.8% for LDV/SOF (24 weeks), and 3.7% for LDV/SOF + RBV (24 weeks).
  - ION-2: 0.0% (no patients) in any treatment group.
  - ION-3: 0% for LDV/SOF (8 weeks), 0.9% for LDV/SOF + RBV (8 weeks), and 0.9% for LDV/SOF (12 weeks).

5.2 Summary of the Clinical Evidence from the Therapeutic Review

CDEC considered the results of CADTH's systematic review and NMA of published literature on interventions of interest for the treatment of CHC infection.[5] The review was an update to the 2014 CADTH TR on DAAs for CHC genotype 1 infection,[7] 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 treatment-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 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; 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 SIM12 + PR for 48 weeks. 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. 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 8 = ledipasvir for 8 weeks; 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; RBV 12 = ribavirin for 12 weeks; RIT = ritonavir; SIM = simeprevir; SIM 12 = simeprevir for 12 weeks; SOF = sofosbuvir; SOF 8 = 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 who were 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 LDV/SOF

The manufacturer submitted a cost-utility analysis over a lifetime horizon (up to 80 years of age) comparing LDV/SOF with SOF + PR, SIM + PR, telaprevir + PR, boceprevir + PR, SOF/RBV, and no treatment from a public-payer perspective, in patients with genotype 1 CHC. The model included nine health states: two states representing non-cirrhotic disease (CHC non-cirrhotic and SVR non-cirrhotic), three states representing cirrhotic disease (compensated cirrhosis, decompensated cirrhosis, and SVR cirrhotic), hepatocellular carcinoma, liver transplant, post-liver transplant, and death. The cohort consisted of a mixture of cirrhotic and non-cirrhotic patients, and separate analyses were conducted for treatment-naive patients, treatment-experienced patients, and patients who had failed treatment with a protease inhibitor.

Natural history transition rates were based on a number of different published studies, including Grishchenko et al.[8] The clinical effectiveness data were taken from the active groups of the pivotal trials for the therapies being evaluated (i.e., a naive indirect comparison). For patients with prior failure to a protease inhibitor, SVR rates from the subgroup of patients experienced with a protease inhibitor in ION-2 and an abstract from Pol et al. were used for LDV/SOF and SOF + PR, respectively. In an alternate analysis, results from a manufacturer-conducted NMA were used to inform comparative effectiveness in treatment-naive patients. Utility data (Health Utilities Index Mark 2 [HUI2] and Mark 3 [HUI3]) were taken from two surveys of a Canadian CHC population (Hsu 2012[9] and John-Baptiste 2009[10]). Resource

utilization was based on clinical trial observations, clinical experts' assumptions, and the literature. Costs were taken from Ontario health care cost sources. The model did not have states for screening and diagnosis, or a reinfection state. The model did not allow an assessment of the cost-effectiveness of 12 weeks LDV/SOF compared with 8 weeks' LDV/SOF in treatment-naive non-cirrhotic patients.

In the base-case analyses, the manufacturer reported that LDV/SOF was dominant compared with active comparators for treatment-naive patients, and associated with an ICUR of $17,928 per QALY gained, compared with no treatment. For treatment-experienced patients, LDV/SOF dominated SOF/RBV and ICURs for LDV/SOF compared with all other comparators were less than $30,000 per QALY. For patients who failed protease inhibitors, the ICURs for LDV/SOF were less than $30,000 per QALY compared with SOF + PR and with no treatment.

CDR identified several limitations with the submitted pharmacoeconomic model:

- The clinical effectiveness parameters used in the model were drawn from non-comparative trials.
- The model structure aggregated fibrosis stages in early disease (F0, F1, F2, and F3) that have very different costs of care. This artificially increases the expected value of eliminating the virus.
- Natural history data for non-cirrhotic to cirrhotic transition appear to be erroneous.
- The cost of anemia was likely overestimated, which would overestimate total cost of comparators and favour LDV/SOF.
    - The duration of PR therapy with the SIM + PR regimen was potentially overestimated treatment-naive patients and those with prior relapse, which would overestimate the cost of SIM + PR and favour LDV/SOF for these populations.
- The utility parameters might not be reliable.

CDR conducted a number of reanalyses, using lower anemia costs, shorter duration of PR in the SIM+PR regimen, and alternate utility values, but was not able to account for all identified limitations, as many of them were related to the structure of the model or fundamental limitations of the evidence base. Therefore, there remains considerable uncertainty in the results:

- In treatment-naive and treatment-experienced non-cirrhotic patients, LDV/SOF is likely to remain cost-effective versus active comparators, although on balance CDR considers that results generated by the model are likely to be an underestimate of the actual ICUR of LDV/SOF versus other comparators.
- In treatment-experienced cirrhotic patients, ICURs for LDV/SOF versus SOF + PR were consistently greater than $50,000 per QALY (with a less than 30% probability that the ICUR would be less than $50,000 per QALY), and the ICUR for LDV/SOF versus SIM + PR increased to $36,000 per QALY. The estimates of the cost-effectiveness of LDV/SOF in cirrhotic treatment-experienced patients are similarly limited by the flaws in the submitted model, and even the CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

At the submitted price of [redacted] per day, for non-cirrhotic genotype 1 patients, an eight-week course of LDV/SOF ([redacted]) is less costly than SIM + PR regimens ($46,002 to $55,502) and less costly than a 12-week course of SOF + PR ([redacted], based on the confidential price submitted to CDR for sofosbuvir). A 12-week course of LDV/SOF ([redacted]) is more costly than SIM with a 24-week course of PR ($46,002) and more costly than a 12-week course of SOF + PR, [redacted] then SIM with a 48-week course of PR ($55,502). For treatment-experienced cirrhotic patients, the cost of a 24-week course of LDV/SOF ([redacted]) is more expensive than all other CHC regimens currently available. 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 following 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 Therapeutic Review report: *Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis*.[11]

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.[7] The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY (ICUR). 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 this report, the manufacturer has provided the list price for DCV and the analyses were re-run using that price for CDEC deliberation. During the course of the TR, the CDR review of ASU was suspended and the drug had 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 8 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 LDV/SOF 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 CHC genotype 1 infection, indicated that LDV/SOF 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 recommendations from the CDR review of LDV/SOF 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 LDV/SOF is cost-effective in patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).

APPENDIX 1: PATIENT 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 therapeutic review (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. As a 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 ribavirin.

Patient groups indicated that, 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 (Peg-IFN). It was noted that it could be beneficial for patients who may be reluctant to initiate a ribavirin-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 Peg-IFN.

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.[12]

The CLF also noted that there is an unmet need for patients who are infected with more than one genotype of the HCV, 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 patients 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 250 mg	Tablet	$665.00	2 X 12.5/75/50 mg OMG/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 plus 1,000 mg to 1,200 mg/day RBV	12 to 24 weeks[a]	55,860 to 111,720	58,905 to 119,028
	400 mg 600 mg		14.50 21.75			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 12 to 24 weeks: 67,000 to 134,000	44,667 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 24 weeks with RBV 142,872
	400 mg	Tablet	654.76	400 mg once daily		55,000 to 110,000	
	400 mg 600 mg	Tablet	14.50 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 600 mg	Tablet	14.50[b] 21.75[b]	1000 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 28 tablets 35 tablets 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 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens/56 to 98 caplets	786.39 786.39 868.96 868.96			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)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 caplets+ 2 pens+ 56 caplets	2652.55[g] 2652.55[g] 2726.00[g] 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 OMB/PAR/RIT + DAS alone for patients with genotype 1b without cirrhosis; 12 weeks of OMB/PAR/RIT + DAS plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks OMB/PAR/RIT + DAS plus RBV for patients with genotype 1a with cirrhosis who had previous null response to PR. Price obtained from AbbVie website.[13]

[b] Yukon Drug Formulary (March 2015)[14] and Ontario Exceptional Access Program (March 24, 2015).[15]

[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 HCV ribonucleic acid 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).[16]

[h] Dosing varies by weight and HCV genotype.

Source: Saskatchewan Drug Benefit (February 2015) prices unless otherwise stated.[17]

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