Common Drug Review
Request for Advice

May 2016

Drug	sofosbuvir (Sovaldi)
Indication	Sofosbuvir is indicated for the treatment of chronic hepatitis C (CHC) virus infection in adult patients with compensated liver disease, including cirrhosis, as follows: • For the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon and ribavirin (PR). • For the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin (RBV).
Manufacturer	Gilead Sciences Canada Inc.
Request for Advice Questions	Should the CDEC recommendation for sofosbuvir (Sovaldi) 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
CUA	cost utility analysis
DAA	direct-acting antiviral
DAS	dasabuvir
DCV	daclatasvir
FACIT-F	Functional Assessment of Chronic Illness 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
OMB	ombitasvir
PAR	paritaprevir
Peg-INF	pegylated interferon
PR	pegylated interferon plus ribavirin
QALY	quality-adjusted life-year
RBV	ribavirin
RCT	randomized controlled trial
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
TEL	telaprevir
TR	therapeutic review
WPAI	Work Productivity and Activity Impairment Questionnaire

1. BACKGROUND

1.1 Sofosbuvir (Sovaldi)

Sofosbuvir (SOF) is indicated for the treatment of chronic hepatitis C (CHC) infection in adult patients with compensated liver disease, including cirrhosis, for the treatment of genotype 1 and 4 CHC infection in combination with pegylated interferon and ribavirin (PR) and genotype 2 and 3 CHC infection in combination with ribavirin (RBV).[1] SOF is available as 400 mg tablets and the product monograph recommends the following dosage regimens:

- genotypes 1 and 4: SOF 400 mg daily + PR for 12 weeks
- genotype 2: SOF 400 mg daily + RBV for 12 weeks
- genotype 3: SOF 400 mg daily + RBV for 16 to 24 weeks.[1]

1.2 CDEC Recommendation

The recommendation and reasons for the recommendation from the 2014 Canadian Drug Expert Committee (CDEC) recommendation[2] for SOF for the treatment of CHC virus infection state the following:

Recommendation
CDEC recommends that SOF be listed for the treatment of CHC virus infection in adult patients with compensated liver disease, including cirrhosis, if the following clinical criteria and conditions are met: **Clinical criteria:** • Patients with genotype 1 CHC infection, in combination with PR: ▪ a fibrosis stage of F2, F3, or F4 ▪ treatment naive. • Patients with genotype 2 CHC infection, in combination with RBV: ▪ a fibrosis stage of F2, F3, or F4 ▪ previous treatment experience with PR or a medical contraindication to PR. • Patients with genotype 3 CHC infection, in combination with RBV: ▪ a fibrosis stage of F2, F3, or F4 ▪ previous treatment experience with PR or a medical contraindication to PR. **Conditions:** • Reduced price • Funding should not exceed a duration of 12 weeks for the treatment of patients with genotype 1 or 2 CHC and 24 weeks for the treatment of patients with genotype 3 CHC.
Reason(s) for Recommendation
1. A single arm trial (NEUTRINO; N = 327) demonstrated that treatment with SOF + PR achieved high rates of SVR 12 for treatment-naive patients with genotype 1 CHC. In addition, the treatment regimen for SOF has a decreased duration of PR therapy relative to the recommended regimens for other direct-acting antiviral drugs. 2. Four randomized controlled trials (RCTs) (FISSION [N = 499], FUSION [N = 201], POSITRON [N = 280], and VALENCE [N = 419]) demonstrated that treatment with SOF/RBV achieves high rates of SVR 12 for patients with genotype 2 and 3 CHC. 3. At the submitted price ($[redacted] per day), CDEC concluded that SOF + PR is likely to be cost-effective for genotype 1 CHC patients who are treatment-naive and genotype 2 CHC patients who are treatment experienced with PR or have a medical contraindication to PR. However, SOF/RBV treatment may not be cost-effective for some patients with genotype 3 CHC; therefore, a reduction in price is required to support a recommendation for use in patients with genotype 3 CHC who are treatment experienced with PR or have a medical contraindication to PR. 4. For all genotypes, treatment of patients with higher levels of fibrosis is more cost-effective.

CDEC = CADTH Canadian Drug Expert Committee; CHC = chronic hepatitis C; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; SOF = sofosbuvir; SVR = sustained virologic response.

1.3 Conclusions from the 2014 Common Drug Review (CDR) Reports

1.3.1 CDR Clinical Review Report

The primary conclusions for the 2014 *CDR clinical review*[3] were as follows:

There were four randomized controlled trials (RCTs) included in this review that enrolled patients with genotypes 2 or 3 (FISSION, FUSION, POSITRON, VALENCE), but only one single arm study (NEUTRINO) that included patients with genotypes 1 or 4. The genotype 2/3 studies featured a variety of populations and interventions, and with respect to sustained virologic response (SVR)12 responses, the combination of 12 weeks SOF/RBV demonstrated non-inferiority to 24 weeks of PR in a treatment-naive population (FISSION), and superiority to placebo in a population that was ineligible, intolerant, or unwilling to take peginterferon (Peg-IFN) (POSITRON). Subgroup data from FUSION and findings from the descriptive VALENCE study suggest that genotype 3 patients may benefit from a longer duration of SOF/RBV (up to 24 weeks), compared with genotype 2 patients (12 weeks); however, due to design limitations these findings are hypothesis-generating only. The shorter and potentially more tolerable SOF/RBV regimen might be expected to provide relatively better quality of life compared with PR; however, there was no evidence of this from the included studies, in part due to a considerable amount of missing data for this outcome that rendered questionable results.

NEUTRINO lacked a control arm, but SOF + PR was demonstrated to be superior, in terms of SVR, to an external control of 60% in a treatment-naive primarily genotype 1 and 4 population. CDR identified no studies of SOF in treatment-experienced CHC genotype 1 patients that met the criteria for inclusion in this systematic review.

Across all studies, there were no novel safety or tolerability issues that could be attributed to the addition of SOF to either RBV or PR. When compared to PR, SOF/RBV appeared to be more tolerable, as measured by withdrawals due to adverse events.

1.3.2 CDR Pharmacoeconomic Review Report

The primary conclusions of the *CDR Pharmacoeconomic Review* report were as follows:

The incremental cost-utility ratios (ICURs) for SOF versus appropriate comparators varied widely across genotypes and various subgroups. Analyses in genotype 1 patients were limited by lack of direct comparative data. Most of the analyses in genotype 2 and genotype 3 patients were limited by the small sample size of the clinical trials used to inform efficacy inputs. Based on CDR reanalyses, SOF is likely cost-effective in the following subgroups: genotype 1 treatment-naive cirrhotic patients (compared with boceprevir + PR, but analyses were based on very small subgroups, and on a naive indirect treatment comparison); genotype 2 PR-ineligible and prior-relapsers or breakthrough (except cirrhotic patients) compared with no treatment and PR; genotype 3 prior-relapsers or breakthrough with cirrhosis, compared with no treatment and PR.

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. The 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. Ledipasvir/sofosbuvir (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 SOF with the CDEC recommendations from the TR of *Drugs for Chronic Hepatitis C Infection*, CADTH conducted a detailed comparison of the key reasons and evidence underlying each of these recommendations.

4. COMPARISON OF CDEC RECOMMENDATIONS

The CDR review of SOF and the TR included multiple CHC genotypes, each of which were addressed in separate CDEC recommendations (summarized in Table 1).

TABLE 1: COMPARISON OF CDEC RECOMMENDATIONS FOR SOF FROM CADTH CDR REVIEW AND HEPATITIS C THERAPEUTIC REVIEW

Genotype	Treatment Regimen	Recommended Patient Populations	
		CDR Review	Therapeutic Review (Preferred Options)
1	SOF + PR for 12 weeks	• PR-naive (cirrhosis) • PR-naive (no cirrhosis)[a]	• Not recommended
2	SOF/RBV for 12 weeks	• PR-naive[b] (cirrhosis) • PR-naive[b] (no cirrhosis)[a] • PR-experienced (cirrhosis) • PR-experienced (no cirrhosis)[a]	• PR-naive (cirrhosis) • PR-naive (no cirrhosis)[c] • PR-experienced (cirrhosis) • PR-experienced (no cirrhosis)[c]
3	SOF/RBV for 24 weeks	• PR-naive[b] (cirrhosis) • PR-naive[b] (no cirrhosis)[a] • PR-experienced (cirrhosis) • PR-experienced (no cirrhosis)[a]	• PR-naive (cirrhosis) • PR-experienced (cirrhosis)
4	SOF + PR for 12 weeks	• Not reviewed	• PR-naive (no cirrhosis)[c]

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

[a] Restricted to patients with a liver fibrosis stage of ≥ 2.
[b] Restricted to patients with a medical contraindication to PR.
[c] Patients with any stage of liver fibrosis.

4.1 Genotype 1

For patients with genotype 1 CHC infection, CDEC's recommendation in the initial CDR review stated that SOF, in combination with PR, should be listed for treatment-naive patients with a liver fibrosis stage of ≥ 2. CDEC noted in the recommendation document that the therapeutic approach to treating CHC is evolving rapidly and that many highly effective, fully oral regimens of direct-acting antiviral (DAA) drugs without PR or RBV are emerging. For the TR, CDEC recommended two PR-free regimens (LDV/SOF and OMB/PAR/RIT + RTV) as the preferred options for patients with genotype 1. In addition, the TR included a recommendation that all patients with CHC infection should be considered for treatment, regardless of fibrosis score.

4.2 Genotype 2

For patients with genotype 2 CHC infection, CDEC's recommendation stated that SOF, in combination with RBV, be listed for patients with a liver fibrosis stage of ≥ 2 who are PR-experienced or have a medical contraindication to PR. In contrast to the initial CDEC recommendation for SOF, when considering the findings of CADTH's TR, CDEC recommended SOF as the preferred option for patients with genotype 2 CHC regardless of treatment experience, fibrosis stage, or cirrhosis status.

Key differences between the CDR and TR recommendations are as follows:

- The TR recommendations for SOF/RBV are less restrictive than the original CDEC recommendation with respect to the stage of liver fibrosis. Specifically, the TR recommendations do not impose restrictions based on liver fibrosis stage; whereas, the original CDEC recommendation was limited to patients with a liver fibrosis stage of ≥ 2.
- The TR recommendations for SOF/RBV are less restrictive with respect to patients who are PR-naive, as these recommendations no longer contain the clinical criterion that a patient demonstrate a medical contraindication to PR in order to be eligible for treatment with SOF.

4.3 Genotype 3

For patients with genotype 3 CHC infection, CDEC's recommendation stated that SOF, in combination RBV, be listed for patients with a liver fibrosis stage of ≥ 2 who are PR-experienced or have a medical contraindication to PR. The TR recommendations stated that SOF/RBV for 24 weeks is the preferred regimen for patients with genotype 3 CHC who have cirrhosis, regardless of whether or not a patient was previously treated with PR.

Key differences between the CDR and TR recommendations are as follows:

- The TR recommendations for SOF/RBV are somewhat more restrictive than the original CDEC recommendation with respect to the stage of liver fibrosis (i.e., ≥ 2 versus cirrhosis). This is due to the CADTH pharmacoeconomic evaluation demonstrating that DCV + SOF for 12 weeks is more cost-effective than SOF/RBV for 24 weeks for patients with genotype 3 CHC without cirrhosis.
- The TR recommendations for SOF/RBV are less restrictive with respect to patients who are PR-naive, as these recommendations no longer contain the clinical criteria that a patient demonstrate a medical contraindication to PR in order to be eligible for treatment with SOF.

4.4 Genotype 4

Although SOF was indicated for the treatment of genotype 4 CHC at the time of the initial CDR review, the manufacturer did not include this indication in their submission. In the absence of a pharmacoeconomic evaluation for patients with genotype 4 CHC, CDEC was unable to make a recommendation regarding this patient population. In contrast, CADTH included patients with genotype 4 CHC in the TR and CDEC recommended that SOF + PR for 12 weeks is the preferred treatment option for PR-naive patients without cirrhosis. CDEC concluded that there was insufficient evidence to make a recommendation for the following genotype 4 CHC patient populations:

- PR-naive patients with cirrhosis
- PR-experienced patients with or without cirrhosis.

5. CLINICAL EVIDENCE

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

CDEC considered the following information during their deliberations on 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 five patient groups that responded to the CDR call for patient input:

- Hepatitis C is a serious and potentially life-threatening liver disease that is contracted through blood-to-blood contact with an infected person.
- Debilitating physical symptoms may develop, such as chronic fatigue, mental confusion, memory loss, and mood swings that can result in job loss and a reliance on disability benefits or social assistance.
- The lives of caregivers and family members are made much more difficult when a loved one has CHC. They often assume greater financial and child-care responsibilities and worry about their own risk of infection. Family break-up is common.
- People living with CHC want early and uncomplicated access to affordable treatments that have tolerable side effects and that cure the disease in patients with all genotypes. They also want treatments that are shorter in duration than the current treatment periods and a reduced pill burden. Many are waiting for IFN-free or RBV-free therapies to avoid the adverse events associated with those drugs.
- Patients who were not cured with other CHC treatments want the opportunity to be treated with SOF.

5.1.2 Clinical Trials

The CDR systematic review included five studies. One single arm study (NEUTRINO [N = 327]) included patients with genotypes 1, 4, 5 and 6, while the others (FISSION [N = 499], FUSION [N = 201], POSITRON [N = 280], and VALENCE [N = 419]) included patients with genotypes 2 and 3. FISSION was an open-label non-inferiority RCT that compared 12 weeks of SOF/RBV with 24 weeks of PR in a treatment-naive population. FUSION was a double-blind RCT that compared 12 weeks of SOF/RBV with 16 weeks of SOF + RBV, in patients who had failed prior treatment with Peg-IFN, with or without RBV. POSITRON was a double-blind RCT that compared 12 weeks of SOF/RBV with placebo, in a population of patients who were intolerant, unwilling, or ineligible for Peg-IFN therapy. VALENCE was initially designed as a double-blind RCT comparing 12 weeks of SOF/RBV with placebo in a mixed treatment-naive and treatment-experienced patient population. After a protocol amendment during the study, the placebo group was halted and the duration of SOF/RBV was extended to 24 weeks for patients with genotype 3, but remained 12 weeks for patients with genotype 2.

5.1.3 Outcomes

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

- SVR 12—defined as hepatitis C virus (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 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, and role limitations due to physical and emotional challenges. SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS).
- 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, systemic symptoms, and CLDQ total score. All domains and the total score are based on a Likert scale of 0 (worse) 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. The non-inferiority margin for the primary outcome in FISSION was –15%.

5.1.4 Efficacy

a) Genotypes 1 and 4

- The proportion of the total patient population in NEUTRINO that achieved SVR 12 (91%) was statistically significantly greater than an external control of 60% ($P < 0.001$). SVR responses were highest with genotypes 4, 5, and 6 (97%), followed by genotype 1a (92%) and 1b (82%). In the overall population, the proportion of SVR 12 responders was 80% in patients with cirrhosis and 93% in patients without cirrhosis.
- The (mean and standard deviation [SD]) changes from baseline in the NEUTRINO study for SF-36-PCS (–6.5 [9.8]), SF-36-MCS (–6.9 [10.6]), CLDQ-HCV (–0.6 [1.0]), and FACIT-F (–19.8 [25.1]) were statistically significantly lower (worse) at end of therapy compared with baseline. The WPAI reported a mean (SD) increase in the percentage of overall impairment of 22.1% (31.6) for work and 22.0% (31.3) for activity.

b) Genotypes 2 and 3

- The proportion of patients with SVR 12 was reported as follows:
  - FISSION: there was a similar proportion of SVR 12 responders in the SOF/RBV and Peg-IFN/RBV groups (67% in each group, with a between-group difference of 0.3% [95% confidence interval [CI], –7.5% to 8.0%]). The criterion for non-inferiority was met; however, superiority of SOF/RBV versus Peg-IFN/RBV was not demonstrated.

  - FUSION: a statistically significantly greater proportion of patients treated with 16 weeks of SOF/RBV had an SVR 12 compared with those treated with 12 weeks of SOF/RBV (73% versus 51%, with a difference in proportions of –22% [95% CI: –34% to 10%], $P < 0.001$).
  - POSITRON: a statistically significantly greater proportion of patients treated with SOF/RBV had an SVR 12 response compared with those in the placebo group (78% versus 0%, difference in proportions of 77% [95% CI: 71% to 84%], $P < 0.001$).
  - VALENCE: the proportion of patients with an SVR 12 was 93% for genotype 2 patients treated for 12 weeks with SOF/RBV and 85% in genotype 3 patients treated for 24 weeks with SOF/RBV. There were no responders in the 85 patients treated with placebo; the proportion of SVR 12 responders in the genotype 3 group treated with 12 weeks of SOF/RBV was 27%.
- The proportion of patients experiencing relapse was reported as follows:
  - FISSION: 30% with SOF/RBV versus 21% with PR (relative risk [RR] 1.40; 95% CI: 1.02 to 1.93), $P = 0.04$.
  - FUSION: 27% in the 16-week SOF/RBV group versus 47% in the 12 week; RR 1.72 (95% CI: 1.16 to 2.53), $P = 0.006$.
  - POSITRON: 21% with SOF/RBV and a placebo-relapse proportion could not be calculated as there were no responders in this group.
  - VALENCE: 7% for genotype 2 patients taking 12 weeks of SOF/RBV and 14% for genotype 3 patients taking 24 weeks of SOF/RBV.
- Changes in SF-36 were reported as follows:
  - FISSION: The mean (SD) change from baseline in the SF-36-PCS was 0.5 (8.7) in the SOF/RBV group and –4.3 (9.3) in the PR group ($P < 0.001$). The mean (SD) change from baseline in the SF-36-MCS was –3.7 (11.5) and –8.1 (12.8) for SOF/RBV and PR ($P = 0.012$).
  - FUSION: there was no statistically significant difference between the 16-week and 12- week SOF/RBV regimens in either the SF-36-PCS ($P = 0.14$) or SF-36-MCS ($P = 0.17$).
  - POSITRON: There was no statistically significant difference between SOF/RBV and placebo for changes in the SF-36-PCS ($P = 0.57$) or SF-36-MCS ($P = 0.12$).
- FUSION was the only study to report the CLDQ-HCV, FACIT-F, and WPAI-Hep C; there were no statistically significant differences between treatments in changes from baseline for any of these measures.

5.1.5 Harms

- The proportion of patients who experienced at least one adverse event was reported as follows:
  - NEUTRINO: 95% with SOF/RBV for 12 weeks.
  - FISSION: 86% with SOF/RBV for 12 weeks and 96% with PR.
  - POSITRON: 89% with SOF/RBV and 78% with placebo.
  - FUSION: 89% with SOF/RBV for 12 weeks and 88% with SOF/RBV for 16 weeks.
  - VALENCE: 86% with SOF/RBV for 12 weeks, 91% with SOF/RBV for 24 weeks, and 72% with placebo.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - NEUTRINO: 1% with SOF/RBV for 12 weeks.
  - FISSION: 3% with SOF/RBV and 1% with PR.
  - POSITRON: 5% with SOF/RBV and 2% with placebo.
  - FUSION: 5% with SOF/RBV for 12 weeks and 3% with SOF/RBV for 16 weeks.
  - VALENCE: 0% with SOF/RBV for 12 weeks, 4% with SOF/RBV for 24 weeks, and 2% with placebo.

- The proportion of patients who withdrew from the trials as a result of adverse events was reported as follows:
  - NEUTRINO: 2% with SOF/RBV for 12 weeks.
  - FISSION: 1% with SOF/RBV and 12% with PR.
  - POSITRON: 2% with SOF/RBV and 4% with placebo.
  - FUSION: 1% with SOF/RBV for 12 weeks, < 1% with SOF/RBV for 24 weeks, and 1% with placebo.

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.[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).
- In genotype 2, there were five studies for treatment-naive patients, and five studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 2).
- In genotype 3, there were three studies for treatment-naive patients, and six studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 3).
- In genotype 4, there were three studies for treatment-naive patients, and two studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 4).

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 (RR range 1.48 to 1.86). LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks significantly improved SVR compared with SOF/RBV for 24 weeks, response-guided therapy with SIM + PR, and SOF + PR for 12 weeks (result was statistically non-significant for OMB/PAR/RIT + DAS for 12 weeks versus SOF + PR for 12 weeks). There

were no statistically significant differences between LDV/SOF for 12 weeks, DCV + SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks.

Results of the subgroup analysis were consistent with those for the overall treatment-naive population, especially for the comparisons between IFN-free regimens; there were no significant differences in SVR 12 among LDV/SOF for 12 weeks, DCV + SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks where these regimens could be compared with one another. 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 SOF8 + LDV8, 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; LDV8 = ledipasvir for 8 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RIT = ritonavir; SOF = sofosbuvir; SOF8 = 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 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; LDV8 = ledipasvir for 8 weeks; LDV 24 = ledipasvir for 24 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; PR12 = 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.

5.2.2 Genotype 2

a) Treatment-Naive

This analysis included five studies and a total of 116 participants. Overall, three different treatment regimens were considered (PR for 24 weeks, SOF/RBV for 12 weeks, and SOF + PR for 12 weeks). Compared with PR for 24 weeks, SOF/RBV for 12 weeks significantly improved SVR; whereas, SOF + PR for 12 weeks was not significantly different from PR for 24 weeks (RRs ranged from 1.13 to 1.20). When

SOF/RBV for 12 weeks and SOF + PR for 12 weeks were compared, no significant difference was identified. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in genotype 2 infection treatment-naive patients that could be incorporated into the CADTH systematic review and NMA. Results of the subgroup analyses were consistent with those for the overall treatment-naive population; however, SOF + PR for 12 weeks could not be included in the subgroup analysis of patients with cirrhosis due to limitations of the data.

Table 4 presents selected results for the subgroup analysis of SVR for treatment-naive patients with genotype 2 infection.

TABLE 4: SELECTED SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-NAIVE PATIENTS WITH GENOTYPE 2 INFECTION

Subgroup	Studies (N)	Main Findings
Patients with cirrhosis	5 (37)	• Compared with PR for 24 weeks, SOF/RBV for 12 weeks significantly improved SVR in genotype 2 treatment-naive patients.
Patients without cirrhosis	6 (278)	• Compared with PR for 24 weeks, only SOF/RBV for 12 weeks significantly improved SVR. • No significant difference in SVR between SOF/RBV for 12 weeks and SOF + PR for 12 weeks.
HIV co-infection	2 (45)	• Data were insufficient for subgroup analyses.

PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

b) Treatment-Experienced

This analysis included four studies and a total of 172 participants. Based on clinical expert opinion, PR therapy was not considered to be appropriate as a comparator in this population. Overall, three different treatment regimens were considered (SOF/RBV for 12 weeks, SOF/RBV for 16 weeks, and SOF + PR for 12 weeks). Neither SOF/RBV for 16 weeks nor SOF + PR for 12 weeks significantly improved SVR compared with SOF/RBV for 12 weeks (RRs ranged from 0.86 to 1.07), but SOF + PR for 12 weeks significantly improved SVR when compared with SOF/RBV for 16 weeks. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in treatment-experienced patients with genotype 2 infection that could be incorporated into the CADTH systematic review and NMA.

Results of subgroup analyses were generally consistent with those for the overall treatment-experienced population, although SOF16 + RBV16 could not be included in the analysis of patients without cirrhosis. As well, there were no data to allow for an analysis of treatment-experienced patients with genotype 2 infection and HIV co-infection.

Table 5 presents selected results from subgroup analyses of SVR for treatment-experienced patients with genotype 2 infection.

TABLE 5: SELECTED SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-EXPERIENCED PATIENTS WITH GENOTYPE 2 INFECTION

Subgroup	Studies (N)	Main Findings
Patients with cirrhosis	4 (172)	No statistically significant differences in SVR between SOF/RBV for 12 weeks, SOF 16 + RBV16 and SOF 12 + PR 12.
Patients without cirrhosis	3 (95)	SOF + PR for 12 weeks did not significantly improve SVR when compared with SOF/RBV for 12 weeks.

PR = pegylated interferon plus ribavirin; PR 12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; RBV 16 = ribavirin for 16 weeks; SOF = sofosbuvir; SOF 12 = sofosbuvir for 12 weeks; SOF 16 = sofosbuvir for 16 weeks; SVR = sustained virologic response.

5.2.3 Genotype 3

a) Treatment-Naive

This analysis included three studies and a total of 237 participants. Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.31 to 1.37), and there were no significant differences between these regimens. It should be noted that SOF + PR for 12 weeks could be brought into the NMA only as part of a sensitivity analysis informed by clinical expert input in which the results of a major trial (BOSON), published in abstract form at the time of the analysis, were incorporated.

Results of subgroup analyses were consistent with those for the overall treatment-naive population, although DCV + SOF for 12 weeks could not be included in the subgroup analysis of patients with cirrhosis due to a lack of data.

Table 6 presents selected results for the subgroup analyses of SVR for treatment-naive patients with genotype 3 infection. Data were insufficient to perform NMAs for patients with genotype 3 infection coinfected with HIV, as only a single study was identified; it reported an SVR rate of 91% in 51 patients treated with SOF 24 + RBV 24.

TABLE 6: SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT -NAIVE PATIENTS WITH GENOTYPE 3 INFECTION

Subgroup	Studies (N)	Main Findings
Patients with cirrhosis	2 (16)	Compared with PR for 48 weeks, SOF/RBV for 24 weeks significantly improved SVR. No significant difference between SOF 12 + PR 12 and SOF/RBV for 24 weeks.
Patients without cirrhosis	3 (221)	Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR. No significant differences between these 3 regimens.

DCV = daclatasvir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

b) Treatment-Experienced

This analysis included five studies and a total of 269 participants. Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.52 to 1.72). No statistically significant differences were observed between these three regimens.

Results of subgroup analyses were consistent with those for the overall treatment-experienced population; however, there were no statistically significant differences in SVR rates in the subgroup of patients without cirrhosis between SOF + PR for 12 weeks and PR for 48 weeks. There was no evidence for DCV + SOF 24 weeks (the approved duration) that could be analyzed in the NMA of patients with genotype 3 infection and cirrhosis.

Table 7 presents results for the subgroup analysis of SVR for treatment-experienced patients with genotype 3 infection. The only studies in treatment-experienced patients with genotype 3 infection and HIV co-infection were two trials of SOF/RBV for 24 weeks (SVR rates were 86% in one study of 49 patients and 94% in the second study of 17 patients).

TABLE 7: SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-EXPERIENCED PATIENTS WITH GENOTYPE 3 INFECTION

Subgroup	Studies (N)	Main Findings
Patients with cirrhosis	4 (88)	Compared with PR for 48 weeks, SOF/RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR. No significant difference between SOF/RBV for 24 weeks and SOF + PR for 12 weeks.
Patients without cirrhosis	5 (181)	Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks and SOF 12 + PR 12 significantly improved SVR. No significant differences between SOF 24 + RBV 24, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks.

DCV = daclatasvir; PR = pegylated interferon plus ribavirin; PR 12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; SOF = sofosbuvir; SOF 12 = sofosbuvir for 12 weeks; SVR = sustained virologic response.

5.2.4 Genotype 4

a) Treatment-Naive

This analysis included three studies involving a total of 87 participants. Compared with PR for 48 weeks, SOF + RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR; whereas, SOF + RBV for 12 weeks was not significantly different from PR for 48 weeks. SOF + PR for 12 weeks was significantly better than SOF + RBV for 12 weeks for improving SVR. The results of the subgroup analyses were consistent with those for the overall treatment-naive population. In non-cirrhotic patients, SOF + RBV for 24 weeks did not significantly improve SVR when compared with PR.

Table 8 presents selected results for the subgroup analysis of SVR for treatment-naive patients with genotype 4 infection. Only two studies reported results for treatment-naive patients with genotype 4 infection and HIV co-infection: one study of SOF + RBV for 24 weeks reporting an SVR rate of 84% in 31 patients; and one study of SOF + PR for 12 weeks reporting an SVR rate of 91% in 23 patients with genotypes 1 through 4.

TABLE 8: SELECTED SUBGROUP ANALYSIS RESULTS FOR SUSTAINED VIROLOGIC RESPONSE FOR TREATMENT-NAIVE PATIENTS WITH GENOTYPE 4 INFECTION

Subgroup	Studies (N)	Main Findings
Patients with cirrhosis	2 (14)	Compared with PR for 48 weeks, SOF + RBV for 24 weeks significantly improved SVR. SOF + RBV for 12 weeks was not significantly different from PR for 48 weeks for improving SVR.
Patients without cirrhosis	2 (45)	There were no statistically significant differences between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks when compared with PR for 48 weeks or to one another.

PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

SOF + PR for 12 weeks is currently the only regimen indicated for patients with genotype 4 infection. Due to a lack of stratified data, SOF + PR for 12 weeks could not be included in the base-case subgroup analysis of patients by cirrhosis status. A sensitivity analysis was undertaken after the draft Clinical Review report was posted for stakeholder feedback, in which SOF + PR for 12 weeks was included in the subgroup analysis of non-cirrhotic patients based on certain assumptions. It was found that SOF + PR for 12 weeks significantly improved SVR in comparison with PR (RR [95% credible interval] 1.48 [1.27 to 1.55]) and that SOF + PR for 12 weeks was not significantly different from SOF + RBV for 12 weeks or SOF + RBV for 24 weeks. The assumptions allowing for the analysis of SOF + PR for 12 weeks in non-cirrhotic patients could not be applied to the subgroup analysis of patients with cirrhosis.

During the course of CADTH's TR, OMB/PAR/RIT + RBV for 12 weeks was submitted to CDR as a pre-Notice of Compliance submission. The regimen received a Notice of Compliance for the treatment of genotype 4 infection in October 2015. Sensitivity analyses were carried out to incorporate the only trial (PEARL-I) that has studied this regimen into the NMA. Evidence was available only for patients without cirrhosis. In treatment-naive patients without cirrhosis, OMB/PAR/RIT + RBV for 12 weeks was significantly better in terms of SVR compared with PR48, and there were no significant differences between this regimen and SOF + RBV for 24 weeks, or SOF + PR for 12 weeks.

b) Treatment-Experienced

This analysis included two studies and a total of 76 participants. There was no statistically significant difference between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks. Results of the subgroup analyses were consistent with those for the overall treatment-experienced population.

In sensitivity analyses incorporating data from the PEARL-I study for OMB/PAR/RIT + RBV for 12 weeks into the NMA for treatment-experienced patients without cirrhosis, there were no significant differences between OMB/PAR/RIT + RBV for 12 weeks and SOF + RBV for 24 weeks. No evidence was available for this regimen in treatment-experienced patients with cirrhosis.

5.2.5 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, 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 Sofosbuvir

The manufacturer submitted a cost-utility analysis (CUA) conducted over a lifetime horizon. The base-case analysis was comprised of 24 subgroups (genotypes 1, 2, or 3); cirrhosis (presence or absence), and previous treatment exposure (treatment naive, treatment experienced, IFN ineligible, unwilling/intolerant). In genotype 1 treatment-naive patients, SOF + PR for 12 weeks was compared with telaprevir + PR, boceprevir + PR, and PR alone. In genotype 2 patients, SOF + RBV for 12 weeks was compared with PR alone or no treatment. In genotype 3 patients, SOF + RBV for 16 weeks was compared with PR alone or no treatment.

For efficacy data, in genotype 1 patients, in the absence of a comparator group in NEUTRINO, for the base-case analysis, SVR rates were sourced from the intervention group of SPRINT-2 and ADVANCE for telaprevir and boceprevir, and from IDEAL for PR (naive indirect treatment comparison). In a sensitivity analysis, comparative SVR rates from a manufacturer-funded unpublished NMA in non-cirrhotic patients were used. In genotype 2 and 3 patients, SVR rates with SOF were based on POSITRON (IFN ineligible) and FUSION (treatment experienced), while SVR rates for PR were based on historical controls and SVR rates for no treatment were based on POSITRON (IFN ineligible) or assumed to be 0% (treatment experienced). Frequency of adverse events (anemia, depression, and rash), irrespective of severity, was sourced from clinical trials or product monographs. The cumulative incidence of complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) during a patient's lifetime was forecasted using transition probabilities drawn from the literature. Health state utility values were derived from a Canadian study by Hsu et al.[8] Utility decrement during antiviral therapy and utility increment following SVR were applied. Drug costs for comparators were obtained from the Quebec drug formulary. Costs to manage adverse events were obtained from a study using Quebec administrative databases. Liver disease health state costs were derived from a Canadian study on hepatitis B by Dakin et al.[9]

The manufacturer reported that for all genotypes and subgroups, SOF in combination with PR or RBV alone was economically attractive versus comparators, except in genotype 2 prior non-responders with cirrhosis, genotype 3 IFN ineligible or intolerant patients with cirrhosis, and genotype 3 prior non-responders without cirrhosis.

CDR identified a number of limitations with the manufacturer's analyses:

- The design of NEUTRINO and FUSION required the use of historical controls and naive indirect comparisons, which generates uncertainty in the comparative efficacy of SOF with other DAA drugs and PR.
- There was uncertainty in the results of the NMA used by the manufacturer for a sensitivity analysis in genotype 1 non-cirrhotic patients.

- Many of the clinical comparisons were based on small sample sizes and the results in some subgroups were not consistent with the overall findings from FUSION and POSITRON (e.g., patients with cirrhosis presenting better SVR rates than those without cirrhosis).
- The potential longer duration of therapy with SOF in genotype 3 patients (24 weeks instead of 16 weeks) was not considered.

CDR performed additional sensitivity analyses to test the impact of the identified areas of uncertainty considering the following input parameters: Saskatchewan Drug Benefit costs, more conservative SVR estimates, the utility increment assigned to patients who achieved SVR was reduced from 0.08 to 0.07, the time horizon shortened to 80 years of age instead of 100, and a lower cost of anemia.

- In genotype 1 treatment-naive patients without cirrhosis, the cost-effectiveness of SOF versus telaprevir, boceprevir, and PR is uncertain, due to a lack of a direct comparator group in the NEUTRINO trial, and wide credible intervals in the manufacturer's NMA. Using results from the NMA, the ICUR for SOF versus PR, telaprevir, and boceprevir were $50,266 per quality-adjusted life-year (QALY), $11,531 per QALY, and $14,030 per QALY respectively. Using conservative SVR estimates (lower bound of the 95% credible interval from the NMA for SOF), the ICUR for SOF versus PR was $135,391 per QALY, and SOF was dominated by telaprevir and boceprevir. In patients with cirrhosis, using the lower bound of the 95% CI for SOF and assuming a 15% higher SVR rate for telaprevir and boceprevir, the ICUR for SOF was $7,119 per QALY versus PR and $3,237 per QALY versus boceprevir, but was dominated by telaprevir.
- In genotype 2 patients ineligible to receive PR, ICURs for SOF versus no treatment remained under $30,000, regardless of cirrhosis status ($28,983 and $3,268 per QALY respectively). In genotype 2 patients with prior relapse/breakthrough, ICURs for SOF ranged from $23,944 to $31,487 per QALY versus no treatment and versus PR, except in patients with cirrhosis where the ICUR was $62,162 versus PR. In genotype 2 prior non-responders, the ICURs for SOF compared with no treatment or PR were less attractive in patients without cirrhosis (ranging from $61,564 to $136,936), and SOF was dominated by PR and no treatment in patients with cirrhosis.
- In genotype 3 patients ineligible to receive PR, ICURs for SOF versus no treatment were above $75,000 per QALY, regardless of cirrhosis status. In genotype 3 patients with prior relapse/breakthrough, SOF was either dominated or resulted in ICURs > $150,000 per QALY versus no treatment and versus PR in patients without cirrhosis, but resulted in ICURs below $31,000 per QALY in patients with cirrhosis. In prior non-responders, compared with no treatment and PR, SOF was either dominated, or had ICURs above $150,000 per QALY.

At the submitted price of [redacted] per day, for genotype 1 patients, the cost of a 12-week course of SOF is [redacted], which is more costly than a 12-week course of simeprevir ($39,605, including wholesaler mark-up as simeprevir was not listed on any participating drug plans at the time of the SOF review) or telaprevir ($34,968), or a 24-week course of boceprevir ($25,200), but less costly than a 44-week course of boceprevir ($46,200).

When considering the cost of treatment regimens for genotype 1 patients (treatments used in combination with PR), SOF (with a 12 week course of PR, [redacted]) is more costly than simeprevir or telaprevir with a 24-week course of PR (approximately $49,110 and $44,470, respectively), as well as a 24-week course of boceprevir with a 28 or 48-week course of PR (approximately $36,280 and $44,200, respectively), but less costly than simeprevir or telaprevir regimens with a 48-week course of PR (approximately $58,610 and $53,970, respectively), and a 44-week course of boceprevir with a 48-week course of PR (approximately $65,200).

For genotype 2 patients, the cost of a 12-week course of SOF is [redacted], which is more costly than a 24-week or 48-week course of PR ($9,300 to $20,500). For genotype 3 patients, the cost of a 16-week or 24-week course of SOF is [redacted] or [redacted] respectively, which is more costly than a 24-week or 48-week course of PR ($9,300 to $20,500). 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, 2, 3, or 4 CHC. For complete details and results see the following CADTH report: *Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis*.[10]

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 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, response-guided therapy with SIM + PR was likely to be the most cost-effective option, followed by LDV/SOF + RBV for 12

weeks compared with PR alone. The incremental QALYs for OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks compared with PR were similar in all analyses.

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.

6.2.2 Genotype 2

For patients with genotype 2 CHC infection, who are treatment-naive and non-cirrhotic, the IFN-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis and those who are treatment-experienced without cirrhosis, SOF + RBV for 12 weeks was the most cost-effective option, with an ICUR of less than $60,000 per QALY (versus PR for treatment-naive patients, and versus no treatment for treatment-experienced patients). For patients who are treatment-experienced with cirrhosis, SOF + PR for 12 weeks was the most cost-effective option when compared with no treatment (ICUR of $18,226 per QALY), but it is currently not approved for this population; SOF + RBV for 12 weeks was the most cost-effective option that is approved in Canada (ICUR $21,338 per QALY).

6.2.3 Genotype 3

In the base-case analysis for genotype 3 infection, the IFN-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone for treatment-naive patients without cirrhosis (ICURs exceeded $150,000 per QALY). In patients who are treatment-naive with cirrhosis, SOF + RBV for 24 weeks was the most cost-effective approved option at an ICUR of $92,117 when compared with PR for 48 weeks. For patients who are treatment-experienced with or without cirrhosis, SOF + RBV for 24 weeks was the most cost-effective approved option (ICUR approximately $40,000 per QALY compared with no treatment). In exploratory analyses where DCV/SOF for 12 weeks was included in analyses of patients without cirrhosis regardless of treatment experience, this regimen was the most cost-effective among the approved regimens (ICURs $28,151 and $97,158 per QALY for treatment-experienced and treatment-naive patients respectively). However, the unapproved regimen SOF + PR for 12 weeks was the most cost-effective regimen versus PR in treatment-naive patients with genotype 3 infection (ICUR $70,792 per QALY), and versus no treatment for treatment-experienced patients, regardless of cirrhosis status (ICURs for patients with and without cirrhosis < $21,000 per QALY). In relation to SOF + PR for 12 weeks, the most cost-effective approved treatments for genotype 3 infection were either associated with very high ICURs, or were dominated.

6.2.4 Genotype 4

In the base-case analysis for patients with genotype 4 infection who are treatment-naive, no DAA-based regimen was found to be cost-effective in patients without cirrhosis (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis or those who are treatment-experienced, SOF + RBV for 24 weeks was considered the most cost-effective treatment (ICUR less than $60,000 per QALY), but is not currently indicated. SOF + PR for 12 weeks, the only approved treatment for genotype 4 infection, was included in an exploratory analysis of treatment-naive, non-cirrhotic patients with genotype 4 infection; this regimen was associated with an ICUR of $63,421 per QALY compared with PR.

7. CONCLUSIONS

The differences between the CDEC recommendations from the CDR review of SOF and the CDEC recommendations from the TR are primarily a reflection of the rapidly evolving approach to the treatment of CHC, the inclusion of additional SOF indications in the TR, and the inclusion of additional comparators in the pharmacoeconomic evaluation. As CDEC predicted in the initial CDEC recommendation for SOF, the emergence of all-oral DAA regimens led to exclusion of SOF + PR from CDEC's recommended regimens for genotype 1. The preference for all-oral therapy is also reflected in CDEC's recommendations for SOF/RBV in the treatment of patients with genotype 2 and genotype 3 CHC. In this regard, the TR recommendations are less restrictive than the recommendations from the CDR review with respect to patients who are PR-naive, as it is not stated that a patient must demonstrate a medical contraindication to PR in order to be eligible for treatment with SOF. In contrast to the initial CDR review of SOF, CADTH's pharmacoeconomic evaluation demonstrated that SOF + RBV is less cost-effective than DCV/SOF for genotype 3 CHC patients without cirrhosis; therefore, CDEC did not recommend SOF + RBV as a preferred option for these patients. Finally, the inclusion of patients with genotype 4 CHC in the TR led to a favourable recommendation for SOF + PR for use in this patient population, which had previously been excluded from the manufacturer's CDR submission for SOF.

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 therapeutic 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 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 Peg-INF. 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 RBV 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.[11]

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 HCV 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 manifestations 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 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 600 mg		14.50 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 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]	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 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; Peg-IFN = pegylated interferon; 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.[12]

[b] Yukon Drug Formulary (March 2015)[13] and Ontario Exceptional Access Program (March 24, 2015).[14]

[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 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).[15]

[h] Dosing varies by weight and HCV genotype.

Source: Saskatchewan Drug Benefit (February 2015) prices unless otherwise stated.[16]

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