Common Drug Review
Request for Advice

May 2016

Drug	daclatasvir (Daklinza)
Indication	• In combination with other agents for the treatment of chronic hepatitis C (CHC) infection in adult patients with hepatitis C virus (HCV) genotype 1, and 2 infection and compensated liver disease (including cirrhosis)[a] Notice of Compliance (NOC) with conditions: • In combination with other agents for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis.
Manufacturer	Bristol-Myers Squibb Canada Inc.
Request for Advice Questions	Should the CDEC recommendation for daclatasvir (Daklinza) be updated to align with the CDEC recommendations from the CADTH Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*?

[a]Not approved for treatment-experienced patients with genotype 2 HCV and cirrhosis.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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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
CLF	Canadian Liver Foundation
CrI	credible interval
DAA	direct-acting antiviral
DAS	dasabuvir
DCV	daclatasvir
EQ-5D	EuroQol-5 Dimension
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
RIT	ritonavir
RNA	ribonucleic acid
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

1. BACKGROUND

1.1 Daclatasvir (Daklinza)

Daclatasvir (DCV) is a direct-acting antiviral (DAA) drug against the hepatitis C virus (HCV) that is a highly selective inhibitor of the HCV nonstructural protein 5A (NS5A) replication complex. DCV has a Notice of Compliance (NOC) for the following Health Canada-approved indications: in combination with other agents for the treatment of chronic hepatitis C (CHC) infection in adults with HCV genotype 1, and 2 infection and compensated liver disease (including cirrhosis).

DCV has an NOC with conditions (NOC/c) for the following indication: use in combination with other drugs for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis. In accordance with the manufacturer's listing request, the 2015 CDEC recommendation for DCV was limited to the genotype 3 indication.

DCV is available as 30 mg and 60 mg tablets. The recommended dose is 60 mg once daily in combination with sofosbuvir (SOF) for 12 or 24 weeks, with the duration determined by the HCV genotype, prior treatment experience, and the presence of cirrhosis:

- 12 weeks for genotype 1 or 3 (treatment-naive or experienced) without cirrhosis
- 24 weeks for genotype 1 or 3 (treatment-naive or experienced) with cirrhosis
- 24 weeks for genotype 2 (treatment-naive) with or without cirrhosis
- 24 weeks for genotype 2 (treatment-experienced) without cirrhosis.

The addition of ribavirin (RBV) can be considered for patients with genotype 2 or 3 HCV and compensated cirrhosis. The product monograph states that the safety and efficacy of DCV have not been established in patients with decompensated cirrhosis.

1.2 CDEC Recommendation

The recommendation, reasons for the recommendation, and of note sections from the 2015 Canadian Drug Expert Committee (CDEC) recommendation for DCV for genotype 3 CHC state the following:[1]

Recommendation
CDEC recommends that DCV, in combination with SOF, be listed for the treatment of patients with genotype 3 CHC, if the following clinical criterion and conditions are met: **Clinical criterion:** • Treatment-experienced patients without cirrhosis who have not responded to pegylated-interferon plus ribavirin (PR). **Conditions:** • Prescribing restricted to hepatologists and physicians with experience treating patients with CHC. • Drug plan cost of a treatment course with DCV/SOF should not exceed the drug plan cost of a treatment course with SOF/RBV.
Reason(s) for Recommendation
1. One open-label, uncontrolled study (ALLY-3) demonstrated that a subgroup of treatment-experienced patients with genotype 3 CHC who were treated with DCV/SOF for 12 weeks had high rates of sustained virologic response (SVR 12) (86%; 95% confidence interval [CI], 74% to 94%). 2. Reanalyses of the manufacturer's pharmacoeconomic evaluation demonstrated that treatment with DCV/SOF was cost-effective compared with 24 weeks of SOF/RBV when used in patients with genotype 3 CHC who are treatment-experienced without cirrhosis. However, DCV/SOF was not considered to be a cost-effective option for use in patients with genotype 3 CHC who are treatment-naive and/or have cirrhosis.

Of Note
• The manufacturer's requested listing criteria for DCV/SOF were limited to patients with genotype 3 CHC. • The clinical criterion in this recommendation is not stating that treatment-naive patients with genotype 3 CHC should be treated with PR as a first-line option.

CDEC = CADTH Canadian Drug Expert Committee; CHC = chronic hepatitis C; DCV = daclatasvir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks.

1.3 Conclusions from the 2015 CDR Review Reports

1.3.1 CDR Clinical Review Report

The primary conclusions for the 2015 *CDR Clinical Review* report were as follows:
Based on data from two uncontrolled studies, DCV was associated with high rates of SVR 12 when combined with SOF in patients with genotype 1, 2 or 3 CHC. The data were limited due to the small numbers of patients treated, in particular, those with genotype 1 or 2 CHC, and those with cirrhosis. No high-quality evidence is available on the comparative efficacy and safety of DCV/SOF versus other DAA regimens or combinations currently in use in Canada due to the lack of head-to-head controlled studies and the limitations of the manufacturer supplied indirect treatment comparisons. Combination therapy with DCV/SOF appears to be well tolerated, and was not associated with clinically important decreases in quality of life during treatment. Comparative data, however, are lacking with the current interferon (IFN)-free regimens that have become the standard of care.

1.3.2 CDR Pharmacoeconomic Review Report

The primary conclusions for the 2015 *CDR Pharmacoeconomic Review* report were as follows:
The comparative cost-effectiveness of DCV/SOF differed by genotype, patients' treatment experience (naive or experienced), and cirrhotic status (non-cirrhotic or cirrhotic). Comparative evidence in treatment-experienced patients was only presented for genotype 3.The only population in which DCV/SOF appeared cost-effective compared with existing therapies was in genotype 3 non-cirrhotic treatment experienced patients.

For treatment-naive groups, by genotype:

- Genotype 1: DCV/SOF does not appear to be cost-effective. Existing therapies (simeprevir [SIM] + PR or SOF + PR) appear more favourable with incremental cost-utility ratios (ICURs) around $50,000 per quality-adjusted life-year (QALY) compared with PR alone when combining individual comparisons. This holds for both the non-cirrhotic (F0 to F3) and cirrhotic (F4) subgroups. Comparative cost-effectiveness of DCV/SOF versus IFN-free regimens currently reimbursed is unknown.
- Genotype 2: DCV/SOF appears dominated (higher costs, less QALYs) by SOF/RBV.
- Genotype 3: Whilst some evidence is presented that the DCV/SOF regimen may be associated with better clinical outcomes than SOF/RBV in non-cirrhotic patients (F0 to F3), PR appears a more relevant comparator on cost-effectiveness terms. DCV/SOF does not appear to be cost-effective versus PR.

For treatment-experienced groups, by genotype:

- Genotype 3: DCV/SOF appears to be cost-effective compared with SOF/RBV in non-cirrhotic patients (F0 to F3), but not for patients with cirrhosis who require a longer duration of therapy (F4).

2. REQUEST FOR ADVICE

As part of a CADTH Therapeutic Review (TR) *Drugs for Chronic Hepatitis C Infection*),[2] CDEC issued evidence-informed recommendations[3] in November 2015 to address the optimal use of all currently available IFN-free treatments for CHC infection for multiple genotypes. These recommendations stated the following:

1. All patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.
2. Ledipasvir/sofosbuvir (LDV/SOF) and ombitasvir/paritaprevir/ritonavir + dasabuvir (OMB/PAR/RIT + DAS) ± RBV as preferred regimens for treatment-naive and peginterferon (Peg-IFN) plus RBV for treatment-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: 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 DCV/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

4.1 Genotype 3 without Cirrhosis

The primary difference between CDEC's recommendation from the initial CDR review of DCV/SOF and the recommendations from the TR is the inclusion or exclusion of treatment-naive patients without cirrhosis (Table 1). The CDEC recommendation DCV/SOF included a clinical criterion that stated the combination should be restricted to treatment-experienced patients with genotype 3 CHC without cirrhosis who have not responded to PR. The rationale for this criterion was stated as follows: *Reanalyses of the manufacturer's pharmacoeconomic evaluation demonstrated that treatment with DCV/SOF was cost-effective compared with 24 weeks of SOF/RBV when used in patients with genotype 3 CHC who are treatment-experienced without cirrhosis. However, DCV/SOF was not considered to be a cost-effective option for use in patients with genotype 3 CHC who are treatment-naive and/or have cirrhosis.*

TABLE 1: CDEC RECOMMENDATIONS FOR DCV/SOF FROM THE CDR REVIEW AND HEPATITIS C THERAPEUTIC REVIEW

Genotype	Treatment Regimen	Recommended Patient Populations	
		CDR Review	TR Preferred Options
3	DCV/SOF for 12 weeks	• PR-experienced (no cirrhosis)	• PR-naive (no cirrhosis) • PR-experienced (no cirrhosis)

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; DCV = daclatasvir; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir; TR = Therapeutic Review.

In contrast to the initial CDEC recommendation for DCV/SOF, when considering the findings of CADTH's TR, CDEC recommended DCV/SOF as the preferred regimen for patients with CHC genotype 3 infection without cirrhosis who are treatment-naive or PR-experienced. In consideration of the evidence from the TR, CDEC gave considerable weight to input from patient groups and clinical experts who suggested that Peg-IFN should be avoided, whenever possible, due to its adverse effect profile. In keeping with this, CDEC recommended the most cost-effective Peg-IFN-free regimens.

Furthermore, CDEC noted the following in support of the recommendation that DCV/SOF is the preferred option for patients with genotype 3 CHC infection without cirrhosis (regardless of treatment experience): *DCV/SOF for 12 weeks was associated with lower total costs and slightly higher QALY gains (ranging from 0.10 to 0.18 QALYs) in the cost-effectiveness analysis compared with SOF/RBV for 24 weeks, resulting in the latter regimen being dominated.*

4.2 Genotype 3 with Cirrhosis

The product monograph for DCV recommends the following dosage regimen for treatment-naive or treatment-experienced patients with genotype 3 CHC and compensated cirrhosis: DCV 60 mg daily + SOF 400 mg daily for 24 weeks. However, neither the CDEC recommendation from the CDR review nor the recommendations from the TR stated that DCV/SOF should be listed for use in genotype 3 CHC patients with cirrhosis. CDEC elected to exclude this patient population from the recommendations for DCV/SOF due to the limited evidence available for DCV/SOF in this setting and at the recommended dosage. Specifically, the following issues precluded a recommendation to list DCV/SOF:

- DCV/SOF for 24 weeks has only been studied in treatment-naive patients; clinical trial experience with the DCV/SOF regimen in HCV genotype 2 and 3 infection in treatment-naive patients was extrapolated to treatment-experienced patients.

- The proportion of patients with genotype 3 and cirrhosis who were treated with DCV/SOF for 24 weeks was extremely limited (n = 3).
- CADTH's TR noted that there was also no evidence for DCV/SOF for 24 weeks that could be analyzed in the network meta-analysis (NMA) or cost-effectiveness analysis of patients with genotype 3 infection and cirrhosis.

5. CLINICAL EVIDENCE

5.1 Summary of the Clinical Evidence from the CDR Review of DCV/SOF

CDEC considered the following information during their deliberations on SOF:

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

5.1.1 Patient Input Information

The following is a summary of information provided by five patient groups that responded to the CDR call for patient input:

- CHC infection is a serious and potentially life-threatening disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and death. Patients may experience fatigue, general weakness, abdominal, muscle or joint pain, itchiness, poor circulation, constipation, nausea, loss of appetite, headaches, disrupted sleep, and jaundice. Cognitive functioning is affected in some patients.
- Patients must cope with the stigma associated with CHC infection and are often reluctant to disclose their HCV status for fear of rejection and discrimination.
- Spouses and loved ones who care for patients with CHC infection are faced with a substantial burden, as the symptoms of the infection and side effects of treatment can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children.
- The expectations for DCV are that it will address unmet patient needs. Due to its low toxicity and lack of drug interactions, it is expected that DCV will open up treatment to patients who had contraindications to, or who could not tolerate, IFN-based treatments. Patients see advantages with DCV that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients, high response rates.

5.1.2 Clinical Trials

The systematic review included two open-label, uncontrolled trials in patients with genotype 3 (ALLY-3)[4] or genotype 1, 2, or 3 CHC (study 040) and included both treatment-naive and treatment-experienced cohorts. DCV was combined with SOF for 12 weeks (ALLY-3, 040) or 24 weeks (study 040) with and without ribavirin (RBV). The sample size per treatment cohort ranged from 14 to 101 patients. All trials excluded patients with decompensated liver disease, hepatitis B or HIV co-infection, malignancy, or recent substance abuse.

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.

- EuroQoL 5-Dimensions Questionnaire (EQ-5D) — 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. EQ-5D consists of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) that are converted to a utility score.

The primary outcome in both trials was the proportion of patients who achieved SVR 12.

5.1.3 Efficacy

- Among patients who received DCV/SOF, the proportion of patients with SVR 12 was reported as follows:
  - Study 040: genotype 1 treatment-naive 100% (12 weeks); 100% (24 weeks)
  - Study 040: genotype 1 treatment-experienced 100% (24 weeks)
  - Study 040: genotype 2 or 3 treatment-naive 100% (24 weeks)
  - ALLY-3: genotype 3 treatment-naive 90% (12 weeks)
  - ALLY-3: genotype 3 treatment-experienced 86% (12 weeks).
- In ALLY-3, patients with cirrhosis had a lower SVR 12 rate (58% to 69%, total N = 29) than those without cirrhosis (94% to 97%, total N = 109).
- Among patients who received DCV/SOF + RBV, the proportion of patients with SVR 12 was reported as follows:
  - Study 040: genotype 2 or 3 treatment-naive 86% (24 weeks).
- Relapse was reported in 9% of treatment-naive and 14% of treatment-experienced genotype 3 patients in ALLY-3. No relapses were reported in study 040.
- In ALLY-3, no clinically important changes in quality of life scores were observed at the end of treatment, or 12 weeks after treatment, in patients who received DCV/SOF for 12 weeks.

5.1.4 Harms

- The most commonly reported adverse events for DCV/SOF regimens included headache (20% to 34%), nausea (0% to 36%), and fatigue (14% to 50%). The proportion of patients who experienced at least one adverse event was reported as follows:
  - ALLY-3: 66% to 78% (12 weeks)
  - Study 040: 93% (12 weeks); 76% to 93% (24 weeks).
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - ALLY-3: 0% to 1% (12 weeks)
  - Study 040: 2% (12 weeks); 0% to 14% (24 weeks).
- The proportion of patients who experienced an adverse event leading to discontinuation of any study drug was reported as follows:
  - ALLY-3: 0% (12 weeks)
  - Study 040: 0% (12 weeks); 0% to 7% (24 weeks).

5.2 Summary of the Clinical Evidence from the Therapeutic Review

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

historically controlled studies, such trial designs were included in the review. The main efficacy outcome of interest was SVR 12 or 24 weeks. Key safety outcomes were rash, depression, and anemia.

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). 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 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 lack of data.

Table 2 presents selected results for the subgroup analyses of SVR for treatment-naive patients with genotype 3 infection. Data were insufficient to perform an NMA for patients with genotype 3 infection co-infected 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 2: 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 3 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 3: 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.

5.2.2 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 that was likely at higher risk for comorbid depression compared with the broader population of patients with CHC infection.

For treatment-experienced patients, LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments. For rash there was no significant difference between OMB/PAR/RIT + DAS ± RBV for 12 weeks and LDV/SOF for 12 weeks. For anemia, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than OMB/PAR/RIT + DAS for 12 weeks, and LDV/SOF for 12 weeks. Evidence was limited for depression in treatment-experienced patients. There was insufficient evidence to include DCV/SOF in the analyses of these adverse events for treatment-experienced patients.

6. COST EVIDENCE

6.1 Summary of the Pharmacoeconomic Evidence from the CDR Review of DCV/SOF

The manufacturer submitted a cost-utility analysis assessing the cost-effectiveness of DCV/SOF in treatment-naive and treatment-experienced patients with various genotypes of HCV (genotype 1, 2, or 3) and either cirrhosis status (cirrhotic or non-cirrhotic). The comparators varied by genotype and consisted of DAAs + PR regimens (SOF, SIM, telprevir [TEL], and boceprevir [BOC]), SOF/RBV, and PR alone over a lifetime horizon (up to 100 years of age) from a Ministry of Health perspective. The submission used the Modelling the Natural History of Cost-effectiveness of Hepatitis (MONARCH) model that tracked patients through METAVIR fibrosis states through to decompensated cirrhosis, complications (hepatocellular carcinoma, liver transplantation), and death.[5] Where SVR was obtained, patients moved to a set of SVR-specific states in which relapse to HCV-positive states did not occur and progression was limited only to the case where SVR was obtained following existing compensated cirrhosis. The model did not allow for reinfection or relapse. Most of the model inputs (transition probabilities, utility data, disease-specific costs, costs of adverse events) were based on the 2014 CADTH TR *Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*,[6] which based its inputs on Thein et al. (2008),[7] Hsu et al. (2012),[8] Krajden et al. (2010),[9] and Gao et al. (2012).[10] Drug costs were sourced from the DeltaPA database (IMS Brogan 2014). [11]

The manufacturer reported that a 12-week treatment regimen of DCV/SOF in treatment-naive and treatment-experienced patients with genotype 3 and a fibrosis stage between F0 and F3 is dominant (i.e., less costly and more effective) compared with a 24-week regimen of SOF/RBV. However, in treatment-naive patients, SOF/RBV was not cost-effective versus PR. Given this, the manufacturer's claim of dominance in treatment-naive patients is possibly misleading.

CDR identified several limitations with the manufacturer's pharmacoeconomic submission:

- There is uncertainty in the comparative SVR and adverse event rates for DCV/SOF versus comparators. The manufacturer used matching-adjusted indirect comparisons (genotype 1 treatment-naive, genotype 3) and naive indirect comparisons (genotype 2). In addition, comparative evidence in treatment-experienced patients was limited to genotype 3.
- The manufacturer's model does not allow for a clear comparison of all comparators simultaneously.
- There is a lack of comparison with other available IFN-free regimens (for genotype 1 patients) and no treatment (for all genotypes).
- All-cause mortality risk was not correctly applied in patients with advanced disease, and the probabilistic sensitivity analysis did not adhere to best modelling practices.

CDR reanalyses applying a risk of all-cause mortality to advanced disease health states and modifying the probabilistic sensitivity analysis demonstrated that DCV/SOF did not appear economically attractive in any comparison, except in genotype 3 treatment-experienced patients without cirrhosis compared with 24 weeks of SOF/RBV, where DCV/SOF was dominant.

At the submitted price of [redacted] per tablet, the DCV/SOF 12-week regimen is less costly ([redacted]) than a 24-week course of SOF + RBV ($113,045 to $117,308), but more costly than a 48-week course of PR ($9,437 to $20,855).

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 3 CHC. For complete details and results see the following CADTH report: Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis.

6.2.1 Methods

The cost-utility analysis of drugs for CHC infection was performed using an updated version of the model used for the 2014 CADTH TR of treatments for CHC infection.[6] The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY (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 this drug were not considered by CDEC in developing recommendations. ASU was subsequently approved by Health Canada on March 9, 2016.

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 Results for Patients with Genotype 3 CHC

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.

7. OTHER CONSIDERATIONS

CADTH discussed the CDEC recommendations from the CDR review of DCV and the TR with a clinical expert, who noted that DCV/SOF is currently the only RBV-free regimen approved for use in patients with genotype 3 CHC and, therefore, may address an unmet medical need for patients who have a contraindication or intolerance to RBV.

8. CONCLUSIONS

The initial CDEC recommendation for DCV/SOF included a clinical criterion that treatment should be restricted to treatment-experienced patients with genotype 3 CHC, without cirrhosis, and who have not responded to PR. In contrast, the CDEC recommendations from the TR indicated that DCV/SOF is the preferred regimen for patients with genotype 3 CHC without cirrhosis who are PR-naive or PR-experienced. This difference is attributed to CDEC's preference that Peg-IFN regimens should be avoided, whenever possible, and CADTH's pharmacoeconomic evaluation, which provided greater certainty that DCV/SOF is a cost-effective treatment option for patients with genotype 3 CHC compared with SOF/RBV, the only treatment option approved for use in genotype 3 CHC at the time of the TR.

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 Therapeutic Review (TR) of hepatitis C drugs. In addition, CADTH contacted the patient groups who provided input in the individual CDR reviews and/or the TR and invited them to provide information on the following:

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

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

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

Fibrosis Stage

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

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

Ribavirin

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

Patient groups indicated that, in general, patients are willing to tolerate treatment with RBV in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with RBV are much less severe than those associated with pegylated interferon (Peg-IFN). 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.[12]

The CLF also noted that there is an unmet need for patients who are infected with more than one genotype of the hepatitis C virus (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 a patient with a 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 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 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 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).[16]

[h] Dosing varies by weight and HCV genotype.

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

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