Common Drug Review
Pharmacoeconomic Review Report

September 2015

Drug	daclatasvir (Daklinza)
Indication	In combination with other agents for the treatment of chronic hepatitis C (CHC) infection in adults with hepatitis C virus (HCV) genotype 1, and 2 infection and compensated liver disease (including cirrhosis)[a] Notice of Compliance (NOC) with conditions: Use in combination with other agents for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis.
Listing request	For treatment-naive and treatment-experienced patients (with pegylated interferon plus ribavirin-based therapies) for the following regimen: • Daclatasvir (DCV) plus sofosbuvir (SOF) for genotype 3 CHC
Dosage form(s)	60 mg tablet
NOC date	August 13, 2015
Manufacturer	Bristol-Myers Squibb Canada Inc.

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

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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ABBREVIATIONS

BOC	boceprevir
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
DCV	daclatasvir
G	genotype
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
MAIC	matching-adjusted indirect comparisons
MONARCH	Modelling the Natural History of Cost-Effectiveness of Hepatitis
PR	pegylated interferon plus ribavirin
QALY	quality-adjusted life-year
RBV	ribavirin
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
TEL	telaprevir

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	DCV 60 mg as a component of a combination antiviral treatment regimen			
Study Question	Is the DCV + SOF 12-week or 24-week regimen a cost-effective option when compared with the standard of care antiviral regimens in CHC patients infected with HCV G1, G2, or G3?			
Type of Economic Evaluation	Cost-utility analysis			
Target Population	Patients with CHC G1, G2, or G3 (TN or TE)			
Treatment	• DCV 60 mg once daily plus SOF for 12 wks (G1, G3 without cirrhosis [F0–F3]) • DCV 60 mg once daily plus SOF for 24 wks (G1, G3 with cirrhosis [F4]) • DCV 60 mg once daily plus SOF for 24 wks (G2)			
Outcome(s)	QALYs			
Comparator(s)	**G1**	**G2**	**G3**	
	SOF + PR 12 wks SIM + PR RGT or 48 wks TEL + PR RGT or 48 wks (discontinued) BOC + PR RGT or 48 wks PR 48 wks	PR 24 wks SOF + RBV 12 wks	PR 24 wks SOF + RBV 16 wks (dosage no longer indicated in Canada) SOF + RBV 24 wks	
	Comparisons with the above treatments were not available for all subgroups.			
Perspective	Ministry of Health			
Time Horizon	Lifetime			

Results for Base Case

Comparator	**HCV Genotype**		
	G1 (64%)	G2 (14%)	G3 (20%)
	DCV + SOF Regimen		
	DCV + SOF 12 or 24 wks ($/QALY)	DCV + SOF 24 wks ($/QALY)	DCV + SOF 12 or 24 wks ($/QALY)
SOF + PR 12 wks	TN: > $50,000	NA	NA
SIM + PR RGT or 48 wks	TN: > $50,000	NA	NA
TEL + PR RGT or 48 wks	TN: > $50,000	NA	NA
BOC + PR RGT or 48 wks	TN: > $50,000	NA	NA
PR 48 wks	NA	NA	NA
PR 24 wks	NA	TN: > $200,000	TN: > $90,000
SOF + RBV 12 wks	NA	TN: dominated	NA

	SOF + RBV 16 wks	NA	NA	< $10,000
	SOF + RBV 24 wks	NA	NA	TN and TE: dominant (F0–F3) > $50,000 (F4)
Key Limitations	• Uncertainty with comparative rates of SVR and adverse events. The manufacturer used matching-adjusted indirect comparisons (G1 TN, G3) and naive indirect comparisons (G2). In addition, comparative evidence in TE patients was limited to G3. • The manufacturer's model does not allow a clear comparison of all comparators simultaneously. • Lack of comparison with other interferon-free regimens (for G1 patients) and no treatment (for all genotypes). • Modelling of all-cause mortality in patients with advanced disease, and the probabilistic sensitivity analysis did not adhere to best modelling practices.			
CDR Estimate(s)	○ When compared with other treatment regimens included in the manufacturer's analysis, DCV + SOF did not appear economically attractive in any comparison, except when compared with 24 wks of SOF + RBV in G3 TE patients without cirrhosis, in which case DCV + SOF was dominant (less costly, more effective).			

BOC = boceprevir; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; DCV = daclatasvir; G = genotype; HCV = hepatitis C virus; NA = not available; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; RGT = response-guided therapy; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN= treatment-naive; wks = weeks.

EXECUTIVE SUMMARY

Background

Daclatasvir (Daklinza, DCV) is an inhibitor of the hepatitis C virus (HCV) NS5A replication complex indicated for use in combination with other drugs for the treatment of chronic hepatitis C (CHC) in adult patients with HCV genotypes (G) 1, 2, or 3 (authorization with conditions), and compensated liver disease, including cirrhosis. The recommended dose is 60 mg daily for 12 to 24 weeks, depending on genotype, treatment experience (naive or experienced), and cirrhotic status (non-cirrhotic or cirrhotic) (Table 2).[1]

TABLE 2: TREATMENT REGIMENS OF DACLATASVIR PLUS SOFOSBUVIR AND DURATION BY PATIENT POPULATION

Patient Population	Regimen	Duration (Weeks)
G1 without cirrhosis (TN or TE)	DCV + SOF	12
G1 with compensated cirrhosis (TN or TE)	DCV + SOF	24
G2 without cirrhosis (TN or TE)	DCV + SOF	24
G2 with compensated cirrhosis (TN)	DCV + SOF ± RBV	24
G3 without cirrhosis (TN or TE)	DCV + SOF	12
G3 with compensated cirrhosis (TN or TE)	DCV + SOF ± RBV	24

DCV = daclatasvir; G = genotype; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.
Source: Adapted from August 2015 product monograph.[1]

The manufacturer's submission was initially based on a 12-week duration of DCV plus sofosbuvir (SOF). However, the draft product monograph was updated during the CADTH Common Drug Review (CDR) process and therefore the manufacturer submitted a revised model to account for the 24-week treatment duration recommended for some populations.[2]

The dose of DCV should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4, or increased to 90 mg once daily when co-administered with moderate inducers of CYP3A4.[1] It is available as 30 mg and 60 mg tablets at a confidential price of $[redacted] per tablet. The cost of a course of DCV treatment is $[redacted]. The total cost of a course of DCV + SOF ± ribavirin (RBV) regimen will range from $[redacted] (DCV + SOF for 12 weeks) to $[redacted] (DCV + SOF + RBV for 24 weeks).

The manufacturer's requested listing for DCV as part of a 12- to 24-week regimen in combination with SOF ± RBV is for the treatment of G3 CHC.

Note that all analyses [redacted]

The manufacturer has submitted a cost-utility analysis over a lifetime horizon (up to 100 years of age) from a ministry of health perspective. The analysis assesses the cost-effectiveness of DCV + SOF across treatment-naive and treatment-experienced subgroups with various genotypes of HCV (G1, G2, G3).[3] The comparators varied by genotypes and consisted of direct-acting antiviral agents plus pegylated interferon plus ribavirin (PR) regimens including SOF, simeprevir (SIM), telaprevir (TEL) and boceprevir (BOC), SOF + RBV and PR alone. The submission uses the Modelling the Natural History of Cost-Effectiveness of Hepatitis (MONARCH) model, which tracks patients through Metavir fibrosis states

through to decompensated cirrhosis, complications (hepatocellular carcinoma, liver transplantation) and death. Where sustained virologic response (SVR) is obtained, patients move to a set of SVR-specific states in which relapse to HCV-positive states does not occur and progression is limited only to cases where SVR was obtained following existing compensated cirrhosis.

The manufacturer reported that DCV + SOF dominated (less costly, more effective) a 24-week course of SOF + RBV in treatment-naive and treatment-experienced patients with G3.

In contrast, DCV + SOF did not appear to be cost-effective versus other comparators in treatment-naive patients with G1, G2, and G3.

Summary of Identified Limitations and Key Results

No-treatment and other interferon-free regimens were not included; as such, the cost-effectiveness of DCV + SOF-based regimens compared with these comparators is unknown. Further, the manufacturer's model does not allow a clear comparison of all comparators simultaneously.

Comparative clinical efficacy and rates of adverse events (including discontinuation) were obtained through matching-adjusted indirect comparisons (MAICs) and naive indirect treatment comparisons. Results of the MAICs are difficult to interpret and compare across comparators, as for the same population, the MAICs produce different rates of SVR and adverse events for DCV + SOF, depending on the regimen against which they are compared. Comparative evidence in treatment-experienced patients was presented only for G3.The manufacturer's models did not adhere to best modelling practices; in particular, there were issues with mortality in patients with advanced disease. This issue, as well as an issue around the probabilistic sensitivity analysis, was corrected by CDR for this report.

Conclusions

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 presented only for G3.The only population in which DCV + SOF appeared cost-effective versus existing therapies was in G3 non-cirrhotic treatment-experienced patients.

For treatment-naive groups, by genotype:

- G1: DCV + SOF does not appear to be cost-effective. Existing therapies (SIM + PR or SOF + PR) appear more favourable with incremental cost-utility ratios around $50,000 per quality-adjusted life-year (QALY) compared with PR 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 currently reimbursed interferon-free regimens is unknown.
- G2: DCV + SOF appears dominated (higher costs, fewer QALYs) by SOF + RBV.
- G3: While some evidence has been 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:

- G3: 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).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis that utilizes version 5 of the Modelling the Natural History of Cost-Effectiveness of Hepatitis (MONARCH) model. The MONARCH model[4] classifies fibrosis using Metavir stages (F0 = no fibrosis, F1 = portal fibrosis with no septa, F2 = portal fibrosis with few septa, F3 = portal fibrosis with numerous septa, and F4 = compensated cirrhosis) and follows patients through the fibrosis stages to decompensated cirrhosis, complications (hepatocellular carcinoma, liver transplantation), and death from disease-specific or all-cause mortality. Where sustained virologic response (SVR) is obtained, patients move to a set of SVR-specific states in which a relapse to states of positive hepatitis C virus (HCV) does not occur and progression is limited only to cases where SVR was obtained following existing compensated cirrhosis (see Figure 4).

The submitted analysis does not allow for reinfection following SVR. This may overestimate the value of treatments with higher SVR rates, especially if the reinfection rate could conceivably differ across treatments, due to their characteristics or clinical willingness to use them among patients or clinicians.

A variety of comparators are considered within the submitted model, with these comparators differing by patient subgroups defined by treatment experience (and response within experienced treatment) and HCV genotype (G). Daclatasvir (DCV) + sofosbuvir (SOF) for 12 to 24 weeks is assessed (note that the base case does not consider the potential for adding ribavirin (RBV) in cirrhotic patients with G2 or G3, although this is recommended in the product monograph). Within each patient subgroup, one DCV + SOF regimen is compared with one to five other treatment regimens. These comparators are five regimens based on pegylated interferon plus ribavirin (PR) (in isolation, or in combination with boceprevir [BOC], simeprevir [SIM], SOF, and telaprevir [TEL]), and SOF + RBV. The model does not allow a comparison with no treatment or with other available interferon-free regimens.

Within the economic model, the short-term success of the treatments in helping patients achieve SVR — which was the main focus of the trials — is used to identify the impact on progression and hence the distribution of patients within the model's states. By assigning quality of life to each state, quality-adjusted life-years (QALYs) can be formed and the main outcome of the analysis is cost utility, in terms of an incremental cost-utility ratio.

Most of the model inputs (transition probabilities, utility data, disease-specific costs , costs of adverse events) were based on the recent CADTH therapeutic review *Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1,*[5] which based its figures on Thein et al. (2008),[6] Hsu et al.,[7] Krajden et al. (2010),[8] and Gao et al. (2012),[9] respectively.

2. MANUFACTURER'S BASE CASE

Given the number of comparisons made and subgroups considered within the manufacturer's submission, a brief summary of the evidence is difficult. While the manufacturer's analyses presents only pairwise comparisons, it is optimal to consider all treatment options together to identify which treatment option provides a cost-effective option. The summaries in Appendix 3 will take the average of treatment groups where necessary to provide such a comparison. When this is done, the results from the manufacturer's submission presents a picture in which there appears to be very little uncertainty as to the cost-effective option at a willingness to pay of around $50,000 per QALY. Where incremental cost-utility ratios (ICURs) are found within the model, they are typically below $20,000 per QALY or above $80,000 per QALY, so that there is relatively little uncertainty.

The following figures summarize the apparently optimal choice at threshold values nearing $50,000 per QALY for the treatment-naive and treatment-experienced groups. The figures displayed show: subgroups were used; which comparators appeared in each analysis; and whether treatments were dominated, not cost-effective (but could be for a range of willingness-to-pay values), or highly likely to be cost-effective at $50,000 per QALY.

Detailed results are presented in Appendix 3.

2.1 Treatment-Naive Comparisons

For treatment-naive patients, comparisons were presented for G1, G2, and G3 (Figure 1).

FIGURE 1: SUMMARY OF THE MANUFACTURER'S COST-EFFECTIVENESS COMPARISONS FOR TREATMENT-NAIVE PATIENTS

	DCV+SOF	LDV/SOF	OBV/PTV/RTV and DSV	PR	BOC+PR	SIM+PR	SOF+PR	SOF+RBV	TEL+PR
HCV G1 (F0-F3)	☒	☐	☐	☐	☒	?	?	☐	■
HCV G1 (F4)	☒	☐	☐	☐	☒	☒	☑	☐	■
HCV G2	■	◆	◆	☑	◆	◆	◆	☒	◆
HCV G3 (F0-F3)	☒	◆	◆	☑	◆	◆	◆	■	◆
HCV G3 (F4)	☒	◆	◆	☑	◆	◆	◆	☒	◆

☑ Cost-effective at $50k per QALY
? Possibly cost-effective at $50k per QALY
☒ Not cost-effective at $50k per QALY
■ Dominated
☐ Not included
◆ Not applicable

BOC = boceprevir; DCV = daclatasvir; DSV = dasabuvir; G = genotype; HCV = hepatitis C virus; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

For G1, a rough comparison across pairwise findings across groups would suggest that the ICUR between the SIM + PR and SOF + PR regimens is around $51,000 per QALY for those in F0 to F3. It is reasonable to expect that there is considerable uncertainty as to which of these two treatments is most cost-effective at $50,000 per QALY. For this reason, Figure 1 indicates that both may be cost-effective. In neither the F0 to F3 nor F4 groups does DCV + SOF appear cost-effective.

For G2, DCV + SOF appears dominated (higher costs, less QALYs) by SOF + RBV.

Overall, for the genotypes 1 to 3 comparisons, the case that DCV + SOF is cost-effective appears to be weak, and in one case it is dominated.

Note that while the manufacturer's results report that DCV + SOF is dominant versus SOF + RBV in non-cirrhotic G3 patients, SOF + RBV would not be cost-effective against PR. Given this, the manufacturer's claim of dominance is possibly misleading.

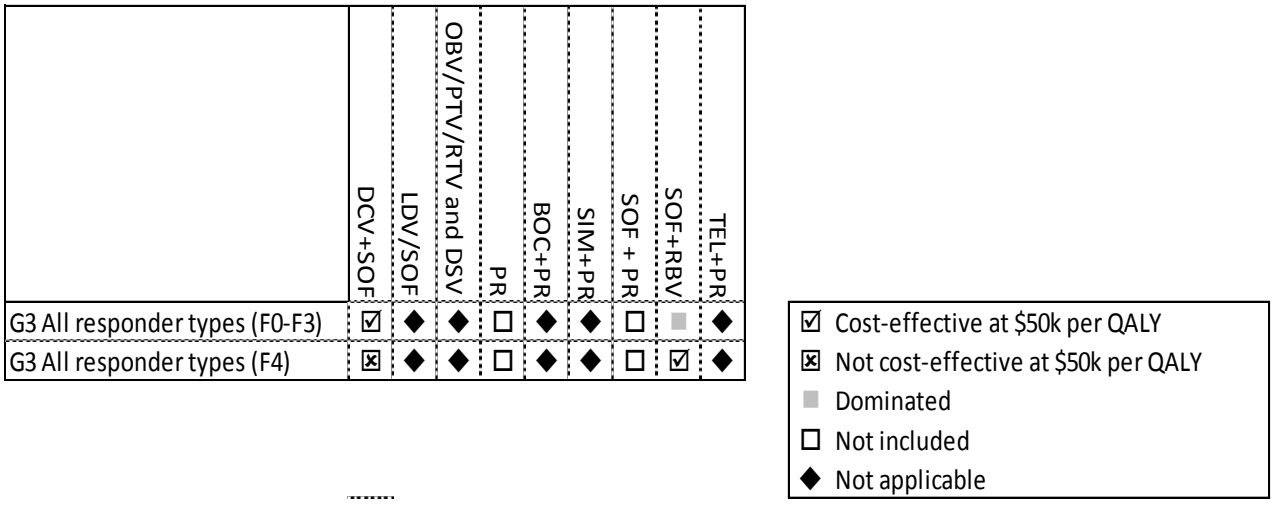
2.2 Treatment-Experienced Comparisons

For treatment-experienced patients, comparisons were presented for G3 (Figure 2).

Evidence for the comparisons here came from one trial.

- AI444218 (ALLY-3)[10] contained 51 treatment-experienced patients with HCV G3. This study indicates that 31 patients had relapsed with PR, 9 had null or partial response to PR, and 11 patients had failed treatment with another type of regimen (including 7 treated with SOF-containing regimens).

FIGURE 2: SUMMARY OF THE MANUFACTURER'S COST-EFFECTIVENESS COMPARISONS FOR TREATMENT-EXPERIENCED PATIENTS



BOC = boceprevir; DCV = daclatasvir; DSV = dasabuvir; G = genotype; HCV = hepatitis C virus; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

For G3, only a single comparison is provided by the manufacturer between DCV + SOF and SOF + RBV. The cost-effectiveness of this appears to differ greatly by the duration of treatment: for non-cirrhotic patients the 12 weeks of treatment with DCV + SOF dominates, while for cirrhotic patients the 24 weeks of treatment has an incremental cost-effectiveness ratio of nearly $120,000 per QALY.

2.3 Summary of Manufacturer's Sensitivity Analyses

The manufacturer's submission contains a probabilistic sensitivity analysis, and explores sensitivity within a series of scenario analyses. These analyses consider both general methodological questions and questions specific to this model:

- mean age at baseline (50 versus 40 and 60 years)
- fibrosis stage distribution
- disease state–specific costs
- transition probabilities
- weekly costs of adverse events
- discount rates (5%, versus 0% and 3%)
- disease state–specific utilities
- alternative efficacy estimates
- scenarios of 30% price reductions of competitive products (SOF, TEL, BOC, and SIM), as well as a scenario where standalone RBV is available for free (100% price reduction).

Unfortunately, the manufacturer's submission does not provide a full account of the results of the sensitivity analyses beyond giving broad statements suggesting the results are largely unchanged.

Even where scenario analyses occur, it is not possible to identify when DCV + SOF might be cost-effective for treatment-naive HCV G1.

The scenario analyses regarding alternative sources of efficacy information are presented more clearly. In all cases, the previously cost-effective option remains so after the changes have been made, suggesting that if the manufacturer's submission is accepted as valid, then these are likely to be cost-effective even under slightly more conservative assumptions.

2.3.1 Daclatasvir Plus Sofosbuvir

- For the treatment-naive HCV G1 patients, the DCV + SOF regimen was not cost-effective when compared with SOF + PR at baseline, with an ICUR of $100,000 per QALY. Since SOF is common to both treatments, we would expect a similar reduction in costs for both comparators, and a broadly similar ICUR. For the non-cirrhotic group (F0 to F3), the ICUR is $111,000 per QALY in both cases. For the cirrhotic group (F4), the ICUR appears to decrease from $233,240 to $184,045 per QALY.
- For G2 patients, the manufacturer's results do not appear to be consistent. While this analysis related to a cost decrease for SOF (which would not be expected to change outcome results), the number of QALYs predicted is noticeably higher in the price discount analysis than in the base case (e.g., for DCV + SOF, 12.37 QALYs in the base case versus 12.62 QALYs in the SOF price discount scenario analysis).

- Similarly, we observe that the expected dominance of DCV + SOF over SOF + RBV would be maintained for treatment-experienced HCV G3 patients. For the treatment-naive HCV G3 patients, DCV + SOF only becomes cost-effective versus PR well above $50,000 per QALY at baseline. While the ICUR for DCV + SOF falls, the general conclusion remains, with DCV + SOF having a high ICUR for PR well above $50,000 per QALY in all cases ($99,000 or $78,000 per QALY in F0 to F3 and $102,000 or $80,000 per QALY in F4).

2.3.2 Addition of Ribavirin to Daclatasvir Plus Sofosbuvir in G2 and G3 Patients With Compensated Cirrhosis

In line with the recommended dose for DCV + SOF, the manufacturers also presented an analysis that included the cost of RBV (i.e., as DCV + SOF + RBV) in patients with subtype G2 and G3 HCV with compensated cirrhosis. This analysis increased the cost of treatment but does not appear to consider any other impacts on safety or efficacy from the addition of RBV. The addition of RBV will increase incremental costs and seems unlikely to improve effectiveness. As DCV + SOF does not appear to be cost-effective in any case other than treatment-experienced, G3 patients *without* cirrhosis, this analysis does not change the conclusions of this analysis.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **There is uncertainty in the comparative efficacy, safety and withdrawal rates of DCV + SOF:** Efficacy (SVR rates) and adverse event rates for the base-case analysis were obtained from matched indirect comparisons (MAIC) and naive indirect comparisons. As stated in the CDR clinical report, there is currently uncertainty as to the performance of MAIC techniques for indirect treatment comparisons. Unlike network meta-analyses, MAICs can only be used to indirectly compare two treatments at a time. Consequently, for the same population, the MAIC produces different SVR rates and adverse events rates for DCV + SOF depending on the regimen against which it is compared. As a result, it is difficult to compare the cost-effectiveness findings for DCV + SOF against other treatment comparators and to combine estimates within a single analysis and consider the likelihood that DCV + SOF is cost-effective against "all-comers," which would represent a gold-standard analysis.

  Where feasible, CDR reviewers identified potential cost-effectiveness results by contrasting findings across individual comparisons. Although this is inherently weaker as an analysis, and does not provide for standard outputs that should be possible with probabilistic sensitivity analyses, it provides an indication beyond the simple pairwise results reported by the manufacturer.

- **The submitted model does not include comparisons with other interferon-free regimens currently approved and/or reimbursed for treatment of G1 CHC:** The majority of CDR-participating drug plans reimburse the ledipasvir/SOF regimen, and many plans recommend it as the preferred therapeutic option over other covered therapies.[11] At the time of this review, Ontario had also announced that ombitasvir/paritaprevir/ritonavir and dasabuvir would be reimbursed as of June 29, 2015.[12] If interferon-free regimens are considered cost-effective (and a preferred option) against existing treatment regimens (direct-acting antivirals + PR and PR), then there should be a comparison against these emerging technologies. Unfortunately, this was not done and so the cost-effectiveness case of DCV + SOF is incomplete. Even among the comparators that are considered, the manufacturer's model does not allow a clear comparison of all options simultaneously.

- **Efficacy inputs do not distinguish between fibrosis stages:** The efficacy inputs were not stratified by fibrosis stage. It is assumed that the comparative effectiveness of DCV + SOF with other regimens is independent of fibrosis stage, which is likely not the case.

- **The submitted model does not include a watchful waiting/no-treatment comparator even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimens.**

- **Some of the components of the manufacturer's model did not adhere to best modelling practices:** A revised version of the model, upon which this report is based, was provided by the manufacturer during the CDR review. Additional shortcomings were identified in the revised model submitted to CDR and are described below:
  - **Mortality:** All-cause mortality was not included in the model for advanced liver disease states (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation) and liver-specific mortality was incorrectly applied. At advanced age, this led to higher survival in the advanced disease group than in groups with more moderate disease.
  - **Reinfection/relapse:** The model assumes that once patients achieve SVR, they are protected from reinfection/relapse for the rest of their lives. From F0 to F3 no complications are possible; from F4, both decompensated cirrhosis and liver cancer are possible but unlikely. The model uses rates of sustained virologic response 12 and 24 weeks after the end of treatment (SVR12, SVR24) from the clinical trials but there is evidence in the manufacturer's submission that patients do relapse within the trial period, and that relapse/reinfection does occur. Aspinall et al. (2013)[13] suggest an annual reinfection rate of around 2.4% for injecting drug users; based on these estimates, after 30 years, half of those successfully treated might be reinfected.
  - **Probabilistic sensitivity analysis:** The probabilistic sensitivity analyses reported by the manufacturer run for only 1,000 iterations, which is not typically enough to provide reassurance that the full range of uncertainty will be captured. The model will also systematically underestimate uncertainty in all parameters in which the same piece of data (e.g., SVR rates) is used many times. This is because the manufacturer's model has "independently" drawn the same parameter multiple times and used these in different places in the model, rather than drawing it once and using this same draw in many places.

- **Uncertainty in CHC health states costs:** CHC health states costs were sourced from Krajden et al.[8] This source was also used in the CADTH therapeutic review *Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*.[5] As noted in the CADTH therapeutic review, these costs were not fibrosis-specific; they may overestimate the cost of mild/no fibrosis and underestimate the cost of severe fibrosis.

3.1 CADTH Common Drug Review Analyses

The manufacturer's submission contains a large number of comparisons and data. These data include a series of comparisons that were of particular interest. Note that TEL has been discontinued. No reanalyses were done for G2 since DCV + SOF was either dominated, or resulted in an ICUR above $200,000 per QALY for all available comparisons in the manufacturer's base case.

FIGURE 3: SELECTED ANALYSES

Genotype 1

- Treatment-naive:
  - DCV + SOF (12 weeks) versus BOC + PR, without (F0 to F3) or with cirrhosis (F4).
  - DCV + SOF (12 weeks) versus SOF + PR, without (F0 to F3) or with cirrhosis (F4).
  - DCV + SOF (12 weeks) versus SIM + PR, without (F0 to F3) or with cirrhosis (F4).

Genotype 3

- Treatment-naive: DCV + SOF versus SOF + RBV (24 weeks) for patients without cirrhosis (F0 to F3) or with cirrhosis (F4).
- Treatment-experienced: DCV + SOF versus SOF + RBV (24 weeks) for patients without cirrhosis (F0 to F3) or with cirrhosis (F4)

BOC = boceprevir; DCV = daclatasvir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir.

3.2 CADTH Common Drug Review Revised Base Case

Some components of the manufacturer's model did not adhere to best modelling practices, mainly the incorporation of all-cause mortality and the probabilistic sensitivity analysis.[2] Upon CDR request, the manufacturer submitted a revised version of the model; however, all-cause mortality remained inadequately incorporated.

The CDR revised base case included the following changes:

- All-cause mortality was incorporated to all health states (including advanced disease states). A detailed explanation of how this was done is provided in Appendix 3.
- The probabilistic sensitivity analysis was modified so that only one random draw was made when a single parameter should apply for multiple cells that would otherwise sample the same parameter multiple times, and which otherwise would place a different value in each cell.
- ICURs are based on the probabilistic sensitivity analysis results, in which the number of iterations was increased from 1,000 to 10,000.

Please refer to Appendix 3, section 5 (CDR Reanalysis) for further details.

Table 3 provides a summary of the manufacturer's results for these comparisons versus those in CDR's corrected base-case analyses.

In the CDR analyses that did not include the specific cirrhosis group (either F0 to F4 or F0 to F3), the general conclusions are very similar to the model as provided by the manufacturer, albeit with slightly lower incremental QALYs for the DCV-containing regiments. In the CDR analyses that did include cirrhosis (F4), the CDR-corrected base case results in much larger differences in incremental costs and consequently higher ICURs than do the manufacturer's analyses.

TABLE 3: COMPARISON OF MANUFACTURER RESULTS AND CADTH COMMON DRUG REVIEW REVISED BASE-CASE ANALYSES

		Manufacturer's Results			CDR Revised Base Case		
	Comparator	Incr. Cost	Incr. QALYs	ICUR ($/QALY)	Incr. Cost	Incr. QALYs	ICUR ($/QALY)
G1, naive (F0–F3)	BOC + PR	$42,664	0.81	$52,385	$42,776	0.82	$52,432
	SOF + PR	$23,122	0.21	$111,376	$23,155	0.21	$111,633
	SIM + PR	$35,931	0.48	$74,977	$35,995	0.48	$74,562
G1, naive (F4)	BOC + PR	$98,273	1.32	**$74,202**	$126,029	1.31	**$95,856**
	SOF + PR	$77,994	0.33	**$233,240**	$105,608	0.33	**$316,893**
	SIM + PR	$91,113	0.77	**$118,408**	$118,781	0.76	**$155,460**
G3, naive (F0–F3)	SOF + RBV	–$32,892	0.06		–$32,888	0.06	
G3, naive (F4)	SOF + RBV	$22,149	0.09	**$259,338**	$50,135	0.08	**$599,435**
G3, experienced (F0–F3)	SOF + RBV	–$32,912	0.13		–$32,900	0.12	
G3, experienced (F4)	SOF + RBV	$22,258	0.19	**$118,975**	$50,229	0.19	**$264,550**

BOC = boceprevir; CDR = CADTH Common Drug Review; DCV = daclatasvir; G = genotype; ICUR = incremental cost-utility ratio; incr. = incremental; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; RGT = response-guided therapy; SIM = simeprevir; SOF = sofosbuvir.
Note: Shaded cells indicated DCV-containing regimen is dominant. All ICURs represent DCV regimen versus the comparator.

3.3 Additional Analyses Using CADTH Common Drug Review Revised Base Case

Of the comparisons presented, a number of comparisons of particular interest were rerun with the models corrected by CDR.

Some analyses conducted prior to the change in recommended duration of DCV + SOF from 12 to 24 weeks in some subgroups were not rerun. These analyses were still based on a cohort of patients with and without compensated cirrhosis (i.e., F0 to F4) receiving 12 weeks of treatment, as these analyses were intended to identify possible sensitivity to inputs and therefore would not be affected by a change in treatment duration.[2]

A series of reanalyses was run:

- incorporating SOF price-reduction scenarios (20% to 40%), with additional threshold analysis
- incorporating health-management costs from Myers et al. (2014)[14] in place of costs from Krajden et al. (2010)[8]
- effects of incorporating adverse event disutilities
- effects of alternative health state utilities.

The reanalyses suggest very little change in the manufacturer's results, as represented by whether or not the DCV-containing regimen appeared to dominate alternatives and by the ICUR in the cases where DCV provided additional health at an additional cost. Further details on these results and individual analyses are presented in Appendix 3.

Sofosbuvir Price-Reduction Scenario
When CDR assumed a price reduction for SOF of 40%, DCV + SOF remained dominant versus 24 weeks of SOF + RBV in the subgroup of G3 treatment-experienced non-cirrhotic patients.

A CDR threshold analysis showed that a 65% price reduction for SOF would result in an ICUR for DCV + SOF versus SOF + RBV of around $46,000 per QALY, while a discount of 66% for SOF leads to an ICUR of $55,000 per QALY for DCV + SOF versus SOF + RBV.

4. ISSUES FOR CONSIDERATION

- All analyses [redacted] an 8-week course of ledipasvir/SOF ($44,667) and a 12-week course of ombitasvir/paritaprevir/ritonavir plus dasabuvir ($55,860).
- Other than PR, SOF + RBV is the only other regimen currently reimbursed by most CDR-participating drug plans for G2 and G3. Of note, most plans cover the SOF + RBV regimen in treatment-experienced patients, but for treatment-naive patients, it is reimbursed only for patients for whom interferon is medically contraindicated.

4.1 Patient Input

Input was received from four patient groups: the Canadian Liver Foundation (CLF), the Canadian Treatment Action Council (CTAC), the Pacific Hepatitis C Network, and the Hepatitis C Education and Prevention Society (HepCBC). Patient groups noted that due to their low toxicity and lack of drug interactions, it is expected that DCV-based regimens will open up treatment to patients who had contraindications to, or who could not tolerate, interferon-based treatments. With a cure, they expect their cirrhosis will reverse and their risk of end-stage liver disease will be reduced. They also expect that some may be able to return to work, and that everyone's quality of life will improve. However, some patients were concerned about side effects, specifically that RBV might be needed for some HCV sufferers. Several patients noted they were deterred from seeking treatment because of the continued presence of RBV in contemporary therapy options.

5. CONCLUSIONS

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 G3. The only population in which DCV + SOF appeared cost-effective versus existing therapies was in G3 non-cirrhotic treatment-experienced patients.

For treatment-naive groups, by genotype:

- G1: DCV + SOF does not appear to be cost-effective. Existing therapies (SIM + PR or SOF + PR) appear more favourable with ICURs around $50,000 per QALY compared with PR 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 currently reimbursed interferon-free regimens is unknown.
- G2: DCV + SOF appears dominated (higher costs, less QALYs) by SOF + RBV.
- G3: While some evidence has been 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:

- G3: 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).

APPENDIX 1: COST COMPARISON

The comparators presented in

Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE FOR DRUGS FOR CHRONIC HEPATITIS C

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) with or without RBV, genotype 1, 2, 3	60 mg	Tab	[redacted][a]	60 mg once daily	12 or 24 weeks[c]	[redacted][a]	[redacted] to [redacted]
	400 mg	Tab	654.7619[b]	400 mg once daily		55,000 to 110,000	24 weeks with RBV
	400 mg 600 mg	Tab	14.5000 21.7500	800 mg daily	24 weeks	4,872	[redacted]
Interferon-free regimens							
Ledipasvir/sofosbuvir (Harvoni)	90/400 mg	Tab	797.6190[b]	90/400 mg once daily	8 to 24 weeks[d]	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)
Ombitasvir/ paritaprevir/ritonavir plus dasabuvir (Holkira Pak)	12.5/75/50 mg 250 mg	Tab	665.0000[b]	25/150/100 mg ombitasvir/ paritaprevir/ritonavir once daily and 250 mg dasabuvir twice daily	12 weeks[e]	55,860	55,860

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (Holkira Pak) plus RBV	12.5/75/50 mg 250 mg	Tab	665.0000[b]	As above plus 1,000 mg to 1,200 mg/day RBV	12 to 24 weeks[e]	55,860	58,905 to 63,168
	400 mg 600 mg		14.5000 21.7500			3,045 to 7,308	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tab	654.7619[b]	400 mg once daily	12 to 24 weeks[f]	55,000 to 110,000	58,045 to 117,308
	400 mg 600 mg		14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 7,308	
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Cap	434.5500	150 mg once daily	12 to 24 weeks[g]	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619[b]	400 mg once daily		55,000 to 110,000	
Direct-acting antivirals in combination with peginterferon alpha plus ribavirin therapy							
Sofosbuvir (Sovaldi) plus PR	400 mg	Tab	654.7619[b]	400 mg once daily	12 weeks	55,000	59,750
	180 mcg/200 mg	Vial/tab	395.8400	Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day	12 weeks	4,750	
Simeprevir (Galexos) plus PR	150 mg	Cap	434.5500	150 mg once daily	12 weeks	36,502	46,002 to 55,502
	180 mcg/200 mg	Vial/tab	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	
Telaprevir (Incivek) (discontinued) plus PR	375 mg	Tab	69.3810	3 × 375 mg two times daily	12 weeks	34,968	44,468 to 53,968
	180 mcg/ 200 mg	Vial/tab	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	
Boceprevir (Victrelis) plus PR	200 mg	Cap	12.5000	4 × 200 mg three times daily	24 to 44 weeks	25,200 to 46,200	37,365 to 67,055
	120 mcg/200 mg	Pens/caps	868.9600	Peg-IFN 1.5 mcg/ kg/week; RBV 800 to	28 to 48 weeks	12,165 to 20,855	

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
				1,400 mg/day[d]			
Boceprevir/P2bR (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 caps + 2 pens + 56 caps	2652.55[b] 2652.55[b] 2726.00[b] 2726.00[b]	Boceprevir 800 mg three times daily; Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 per day[d]	24 to 44 weeks	31,831 to 59,972	31,831 to 59,972
Peginterferon alpha plus ribavirin therapy							
P2aR (Pegasys RBV)	180 mcg/200 mg	Vial or syringe/ 28 tabs 35 tabs 42 tabs	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	9,500 to 19,000
P2bR (Pegetron)	50 mcg/200 mg	2 vials + 56 caps	786.3900	Peg-IFN 1.5 mcg/ kg/week; RBV 800 to 1,400 mg/day[d]	24 to 48 weeks	9,437 to 18,873	9,437 to 18,873
	150 mcg/200 mg	2 vials + 84 or 98 caps	868.9600			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 caps	786.3900 786.3900 868.9600 868.9600			9,437 to 20,855	9,437 to 20,855

cap = capsule; P2aR = pegylated interferon 2a plus ribavirin; P2bR = pegylated interferon 2b plus ribavirin; Peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; tab = tablet.

[a] Manufacturer's confidential submitted price. Note that [redacted] per patient, the manufacturer [redacted].

[b] Ontario Drug Benefit Formulary (June 2015), Exceptional Access Program.

[c] Twelve to 24 weeks of treatment, depending on genotype and cirrhotic status.

[d] Twelve weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. Eight weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment hepatitis C virus ribonucleic acid of less than 6 million IU/mL.

[e] 12 weeks of Holkira Pak alone for patients with genotype 1b without cirrhosis; 12 weeks of Holkira Pak plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks of Holkira Pak plus RBV for patients with genotype 1a with cirrhosis who had previous null response to peg-IFN and RBV.

[f] Genotypes 2 and 3, as well as treatment-naive and non-cirrhotic treatment-experienced patients with genotype 1 ineligible to receive an interferon-based regimen. Twelve weeks for genotype 2, 24 weeks for genotypes 1 and 3.

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

Source: Saskatchewan Drug Benefit (June 2015) prices unless otherwise stated.

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*	Some of the details around the composition of the MAIC was unclear, in particular as it relates to the methods.		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	The efficacy data, and in particular the MAIC provided, do not appear to be credible. Justification of the inclusion of this data was necessary.		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*			

TABLE 6: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☒ Adaptation of Global model/Canadian model done by the manufacturer
☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

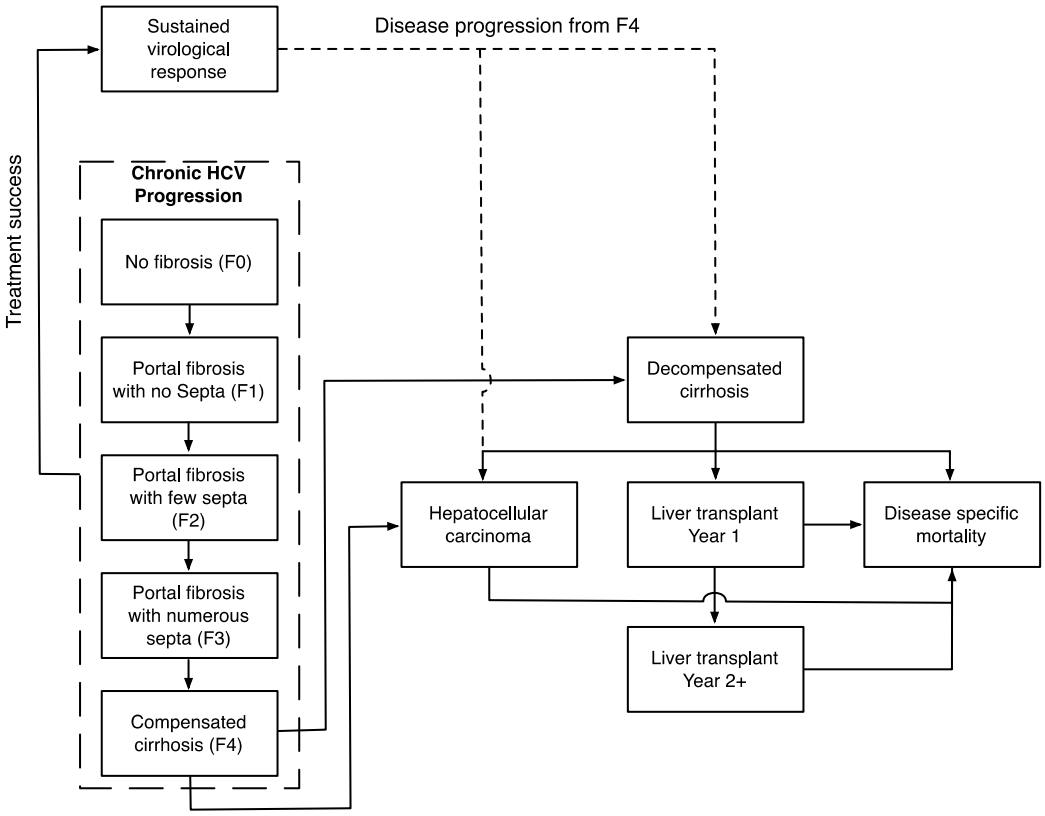
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 3: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

The developed model considers a cohort of patients within a Markov simulation, where the cohort is followed until death. The model allows for transition through progressively more severe chronic hepatitis C virus (HCV) states, through to decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. Where sustained virologic response (SVR) is obtained, the model assumes cure, although it is possible to transition from the most severe fibrosis state (F4) to either hepatocellular carcinoma or decompensated cirrhosis. Version 5 of the Modelling the Natural History of Cost-Effectiveness of Hepatitis (MONARCH) model is relatively flexible, allowing progression to be classified either using fibrosis staging (F0 to F4), or a trichotomous "mild/moderate/severe" categorization. The model as provided by the manufacturer uses fibrosis staging via HCV histology, and so the reproduced figure is an accurate representation of model structure.

FIGURE 4: MANUFACTURER'S MODEL STRUCTURE



HCV = hepatitis C virus.
Source: Manufacturer's pharmacoeconomic submission.[3]

The MONARCH model allows for the use of transition probabilities that are either constant (as used within the model) or dynamic transition probabilities that differ by age. The model allows for a probabilistic sensitivity analysis.

The manufacturer's submission notes the MONARCH model has been used previously in three peer-reviewed publications.[15-17] However, much of the apparent functionality within the MONARCH model has not been utilized within the version of the model provided for this submission. The manufacturer's validation analysis is submitted in Appendix 11 of the pharmacoeconomic submission, which suggests broad comparability in ICURs with the CADTH therapeutic review[5] and progression for patients entering the model in F0 to F4. Notwithstanding this, there are some issues surrounding the calculation of identically distributed items that raise questions as to how accurate the model results may be.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	The main efficacy data are estimated based on indirect treatment comparisons.	For the base case, efficacy (SVR rates) adverse event and discontinuation rates were obtained from naive indirect comparisons, or MAIC, depending on comparisons.
Natural history	Transition probabilities based on Thein et al. (2008).[6]	Two transition probabilities from decompensated cirrhosis to liver cancer and liver transplant states have been added. Neither appears problematic.
Utilities	Hsu et al. (2012)[7] and McLernon et al. (2008),[18] as used in the CADTH therapeutic review.[5] Disutility from adverse events was estimated from Sullivan and Ghushchyan (2006)[19] and Del Rio et al. (2006).[20]	Further details are provided in below the Manufacturer's Key Assumptions section. Note there is no treatment-specific disutility.
Resource use	Not applicable	Pharmaceutical use is based on identified regimens, with the only other costs relating to adverse events. These are covered within the other sections of this table.
Adverse events (anemia and rash)	Based on indirect treatment comparisons	There is no clear single set of estimates for AEs for the DCV + SOF regimens. Further detail on this is given under the Manufacturer's Key Assumptions section.
Mortality	Canadian life tables[21]	These figures are not applied consistently within the manufacturer's model.
Costs		
Drug	DeltaPA database. The cost of DCV [redacted]	No details were provided [redacted]
Administration	No administration costs assumed for pegylated interferon	No comments
AEs	Adverse event costs are assumed to occur only during treatment. Based on Gao et al. (2012)[9] for anemia and rash.	CADTH therapeutic review[5] economic evaluation also included depression, which was not included in the manufacturer's model.
Health state	Based on Krajden et al. (2010)[8] and the CADTH therapeutic review.[5]	Some concerns about appropriateness — see Manufacturer's Key Assumptions.

AE = adverse event; DCV = daclatasvir; MAIC = matched-adjusted indirect treatment comparison; SOF = sofosbuvir; SVR = sustained virologic response.

TABLE 8: TREATMENT COMPARISONS IN THE MANUFACTURER'S MODEL

Genotype	Treatment History	DCV Regimens	Comparators	Type of Comparative Evidence
1	Treatment-naive	DCV + SOF	SIM + PR, TEL + PR, BOC + PR, SOF + PR	MAIC
2	Treatment-naive	DCV + SOF	PR, SOF + RBV	Naive ITC
3	Treatment-naive	DCV + SOF	PR, SOF + RBV	MAIC
	Treatment-experienced	DCV + SOF	SOF + RBV	MAIC

BOC = boceprevir; DCV = daclatasvir; ITC = indirect treatment comparison; MAIC = matched-adjusted indirect treatment comparison; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Natural history and efficacy	
Patients with advanced disease are not subject to all-cause mortality in the model	The model did not allow patients in advanced stages of liver disease (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation) to be subject to all-cause mortality. CDR modified the model so that all-cause mortality was incorporated into all health states (see CDR Reanalysis section that follows).
No recurrence/relapse from SVR	Once a patient achieves SVR, it is assumed the patient is protected from reinfection for the rest of his or her life. From F0 to F3 no complications are possible; from F4, both decompensated cirrhosis and liver cancer are possible but unlikely. Further details are provided in the section below the table.
Distribution of initial cirrhosis stages	It is stated that this comes from the CADTH therapeutic review,[5] although detail is not given. Table 44 in the economic submission appears to have been copied incorrectly and the data in the model spreadsheet differs slightly from the CADTH therapeutic review.
Static transition probabilities	The functionality appears to exist in the model to address issues that would affect the transition probabilities by subgroup (the MONARCH model allows figures to be adjusted for: • duration of infection • proportion of excess alcohol consumption • proportion of intravenous drug users • proportion of HCV patients who contracted via transfusion). However, the submitted model does not appear to do this.
Efficacy figures found via indirect treatment comparisons	Matching-adjusted indirect comparisons and naive indirect treatment comparisons are assumed to provide a coherent evidence base for DCV. See previous table, Data Sources.
Efficacy figures assumed similar across cirrhotic (F0 to F3) and non-cirrhotic (F4) subgroups	This is discussed further in the section following this table.
Costs	
Disease-specific costs classified based on "early-" and "late-" phase cirrhosis	This is discussed in the section following this table.
Identical disease-specific costs for all SVR and cirrhosis states	The mean costs for all non-fibrosis (F0) and fibrotic chronic HCV states (i.e., F0 to F4) and SVR disease from all HCV states (i.e., from

Assumption	Comment
	F0 to F4) are identical. Treatment costs and adverse event costs are additional to this.
Utilities	
Disutility of treatment relates only to adverse events/no treatment-specific disutility.	This is discussed in the section following this table. Note that no disutility (due to AE or treatment-specific) was applied in the base-case analysis, which was a conservative approach.
No differences expected in utilities for F0 to F3	No differences in disutility within early chronic HCV states.

AE = adverse event; DCV = daclatasvir; HCV = hepatitis C virus; MAIC = matched-adjusted indirect treatment comparison; MONARCH = Modelling the Natural History of Cost-effectiveness of Hepatitis; SOF = sofosbuvir; SVR = sustained virologic response.

No recurrence/relapse from SVR: In ALLY-3[22] daclatasvir (DCV) + sofosbuvir (SOF) for G3, a relapse rate of [redacted] patients (of [redacted] initially responding, [redacted]%) was reported. An assumption of zero relapse in the model does not appear to be consistent with the clinical evidence. The indirect treatment comparisons on which the model is based use sustained virologic response 12 or 24 weeks after the end of treatment (SVR12, SVR24). As a result, it is likely that these indirect treatment comparisons will not include those relapses that occur after treatment cessation and so the effectiveness of DCV + SOF is likely to be overstated within model results. This is particularly the case given that SVR12 is preferred to SVR24 where both outcomes are available.

Efficacy and safety figures assumed "similar": Much of the efficacy and safety information in the model is based on matched-adjusted indirect treatment comparisons (MAICs). The comparison between DCV + SOF and SOF + ribavirin (RBV) in G3 is of particular interest, with the MAIC based on work appearing in Appendix 4 of the manufacturer's submission. In the manufacturer's submission, Table 3 of this appendix contains the baseline characteristics of the ALLY-3 and VALENCE trials, which include cirrhosis status as "Yes," "No," and "Not Reported." These figures were different prior to the trial (20.8% cirrhotic for ALLY-3 and 24% cirrhotic for VALENCE) but were weighted to provide a similar finding (24% cirrhotic in both cases).

Cirrhosis status by prior interferon-based treatment is also reported and equalized. It is unclear why, if such weightings are possible, it would not also be possible to use the MAIC to produce separate findings based on both treatment exposure and cirrhosis status (i.e., as F0 to F3, F4). As the appendix does provide findings based on prior interferon exposure, the same could presumably have been done for cirrhosis status.

Disease-specific costs: Disease state–specific costs are based on Krajden et al. (2010),[8] who considered the direct costs of HCV infection (physician services, hospitalization, diagnostic tests, antiviral therapy, and treatment). Within the "default" cost profile provided with the model, a cost of $4,562 is attached to all patients in F0 to F4 or SVR F0 to F4 without any adjustment for severity. For those in the decompensated cirrhosis state and hepatocellular carcinoma states, a value of $14,511 is used. The cost of liver transplantation in the initial and subsequent years is taken from the CADTH therapeutic review.[5]

Utilities: CDR discovered that the "Use AE Disutilities" option in the model (accessible on the "Advanced" button on the "Model Control" sheet) was not selected. This means that the models presented as above did not include the disutilities of adverse events and, as such, there may be a systematic bias against non-injected regimens.

In addition to the issues around adverse events, it is worth noting that methodological uncertainty appears to exist surrounding utility values. The utilities used by the manufacturer give a utility for hepatocellular carcinoma of 0.72, which is above that for decompensated cirrhosis (0.65). In Chong et al. (2003),[23] the carcinoma state has a utility 0.18 *below* decompensated cirrhosis, while Martin et al. (2012)[24] assign the same utility (0.45) to both of these states.

4. Manufacturer's Results

The manufacturer's submission contains a large number of comparisons and a large number of corresponding results. Although not covered in the sections above, it is important to note that the MONARCH model will treat figures that might be expected to be "identical" as "identically distributed." This means that in the probabilistic sensitivity analysis, the deviates drawn from the "same" distribution will, in fact, differ. Values are drawn independently from this distribution for each subgroup of the data. Given this issue, and the concerns raised earlier with respect to the model, little confidence is placed in the specific values obtained.

HCV Genotype 1

Daclatasvir Plus Sofosbuvir in Treatment-Naive Patients (F0 to F3, 12 Weeks)

DCV + SOF appears marginally more cost-effective versus boceprevir on a pairwise comparison ($52,385 per quality-adjusted life-year [QALY]), but the incremental cost-effectiveness of DCV + SOF should be judged against SOF + pegylated interferon plus ribavirin (PR), as this is the next most effective treatment. Against the SOF + PR treatment, the cost-effectiveness is closer to $133,000 per QALY and as such, there seems little question of cost-effectiveness if we can compare findings across the pairwise comparisons.

TABLE 10: MANUFACTURER'S RESULTS FOR DACLATASVIR PLUS SOFOSBUVIR IN TREATMENT-NAIVE GENOTYPE 1 PATIENTS (F0–F3, 12 WEEKS)

Decision Option	Incremental Cost-Effectiveness			
	Comparator	Incremental Costs	Incremental QALYs	ICUR
BOC + PR	BASELINE			
TEL + PR	Dominated			
SIM + PR	Versus BOC + PR	$6,627	0.34	$19,493 per QALY
SOF + PR	Versus SIM + PR	$12,761	0.25	$51,045 per QALY
DCV + SOF	Versus SOF + PR	$23,215	0.18	$132,658 per QALY

BOC= boceprevir; DCV = daclatasvir; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM= simeprevir; SOF= sofosbuvir; TEL=telaprevir.

Daclatasvir Plus Sofosbuvir in Treatment-Naive Patients (F4, 24 Weeks)

Where patients have cirrhosis, the treatment duration is required to be 24 weeks. Given this, the cost of SOF is significantly higher than in non-cirrhotic patients. In this case, DCV + SOF does not appear cost-effective in any single comparison and across the comparators, with an ICUR of more than $250,000 per QALY versus SOF + PR.

TABLE 11: MANUFACTURER'S RESULTS FOR DACLATASVIR PLUS SOFOSBUVIR IN TREATMENT-NAIVE GENOTYPE 1 PATIENTS (F4, 24 WEEKS)

Decision Option	Incremental Cost-Effectiveness			
	Comparator	Incremental Costs	Incremental QALYs	ICUR
BOC + PR	BASELINE			
TEL + PR	Dominated			
SIM + PR	Versus BOC + PR	$6,905	0.56	$12,331 per QALY
SOF + PR	Versus SIM + PR	$12,940	0.39	$33,179 per QALY
DCV + SOF	Versus SOF + PR	$78,184	0.29	$269,600 per QALY

BOC= boceprevir; DCV = daclatasvir; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM= simeprevir; SOF= sofosbuvir; TEL=telaprevir.

HCV Genotype 2

Daclatasvir Plus Sofosbuvir in Treatment-Naive Patients (F0 to F4, 24 Weeks)

The manufacturer's submission compares 24 weeks of DCV + SOF with both PR and with SOF + RBV. DCV + SOF was estimated to be dominated by SOF + RBV (higher costs, lower QALYs), and have an ICUR exceeding $381,000 per QALY when compared with PR. Comparing (again with caution) across the naive indirect comparisons, PR appears the most cost-effective option, since SOF + RBV has an ICUR exceeding $100,000 per QALY.

TABLE 12: MANUFACTURER'S BASE-CASE RESULTS FOR DACLATASVIR PLUS SOFOSBUVIR IN TREATMENT-NAIVE GENOTYPE 2 PATIENTS (F0 TO F4, 24 WEEKS)

Decision Option	Incremental Cost-Effectiveness			
	Comparator	Incremental Costs	Incremental QALYs	ICUR
PR	BASELINE			
DCV + SOF	Dominated			
SOF + RBV	Versus PR	$48,108	0.47	$102,357 per QALY

DCV = daclatasvir; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir.

HCV Genotype 3

Daclatasvir Plus Sofosbuvir in Treatment-Naive Patients

For the F0 to F3 group (12 weeks), DCV + SOF dominates SOF + RBV but has a high ICUR versus PR in the two comparisons provided by the manufacturer (more than $100,000 per QALY). Given this, it does not appear to be a cost-effective alternative.

For the F4 group (24 weeks), DCV + SOF (total costs: $212,000) appears to be significantly more expensive than either PR (total costs: around $82,000) or SOF + RBV (total costs: $188,000); however, across the four comparisons, the average effectiveness of DCV + SOF (11.17 QALYs) is very similar to that of SOF + RBV (11.17 QALYs). In this case, a quick comparison across the cases presented would suggest

that DCV + SOF would be either dominated or extendedly dominated. Even if only SOF + RBV was considered in isolation, here the ICUR would be around $277,000 per QALY.

Daclatasvir Plus Sofosbuvir in Treatment-Experienced Patients

When considering only the F0 to F3 group, DCV + SOF dominates SOF + RBV, at a saving of approximately $33,000 per patient and an increase of around 0.13 QALYs per patient. PR was not included in this analysis.

For the F4 group, the 24-week treatment duration makes the DCV + SOF regimen much more expensive so that, versus SOF + RBV, the daclatasvir-containing regimen costs approximately $119,000 per QALY. In this case, the choice of cost-effective treatment appears to be mostly between SOF + RBV and any other relevant treatment, rather than with DCV + SOF.

Manufacturer's Sensitivity Analyses

The sensitivity analyses within the model are primarily (1) the probabilistic sensitivity analyses and (2) a series of scenario analyses. These analyses consider:

- mean age at baseline (50 versus 40 and 60 years)
- fibrosis stage distribution
- disease state–specific costs
- transition probabilities
- weekly costs of adverse events
- discount rates (5%, versus 0% and 3%)
- disease state–specific utilities
- alternative efficacy estimates
- price-reduction scenarios of competitive products except PR (30% price reduction) and free standalone RBV (100% price reduction).

CADTH Common Drug Review Reanalysis

All-Cause Mortality

The manufacturer's revised model did not allow patients in advanced stages of liver disease (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation) to be subject to all-cause mortality. The use of all-cause mortality is important here: in the version without all-cause mortality, those who survive in these advanced states may survive for a very long time. Within the manufacturer's model, CDR reviewers noticed patients having liver transplants at age 95 and surviving until age 129, when the model ends.

CDR modified the model and all-cause mortality was incorporated for those in advanced states. Patients who die from liver-related causes are identified consistently throughout; anyone who would have died from liver-related causes AND other causes within the same year transition to the liver-related death state. In the version of the model modified by CDR, the assumptions surrounding all-cause mortality mean that all patients die at 100 years of age.

This was done in the following fashion:

- The transition matrices provided by the manufacturer (*before* the changes made to attempt to incorporate mortality) make the transitions among remaining states conditional on the non-liver–related (i.e., "all-cause") mortality not having occurred.

- If a period-specific transition matrix *were* to be formed, it could be calculated in the following way:
  - The absolute probability of a disease state occurring is given by the transition probability provided by the manufacturer multiplied by the probability of all-cause mortality not occurring (i.e., one minus the probability of all-cause mortality).
  - As each row of the transition matrix (without all-cause mortality) summed to one before this change, this absolute probability now sums to one minus the probability of all-cause mortality.
  - Once the probability of all-cause mortality is added to each row, each row now sums to one.
- It is not necessary to actually form this period-specific transition matrix. Instead, calculated probability in the Markov trace (except for all-cause mortality) was multiplied by one minus the period-specific all-cause mortality figure. The per-period mortality was then calculated using this figure and added to the model. This has the same effect in each period as using a period-specific transition matrix but is much simpler to code into the model.

Probabilistic Sensitivity Analysis

The MONARCH model will treat figures that might be expected to be "identical" as "identically distributed." This means that in the probabilistic sensitivity analysis, the deviates drawn from the "same" distribution will, in fact, differ. As an example, for the G1 analysis, efficacy is assumed to be taken from a beta distribution that has a mean value of 0.915 and a standard error of 0.025, and F0 to F4 all use the same data. Values are drawn independently from this distribution for efficacy, so that the efficacy from the F0 to F4 states might be 0.924, 0.886, 0.918, 0.888, and 0.926. The average figure is 0.908. When figures are drawn this way, overall efficacy remains closer to the mean than is appropriate. Splitting parameters that are meant to relate to the whole population in this way would understate the uncertainty in efficacy, and may bias findings of the model.

The CDR reanalyses modified the "PSA deviate" columns so that where it appears that one data source motivates multiple assumptions, only one random draw is made and all the parameters take this value:

'Processed Data'!$K$17:$K$26, 'Processed Data'!$V$17:$V$26, 'Processed Data'!$K$134:$K$135, 'Processed Data'!$K$137:$K$138, 'Processed Data'!$K$167:$K$176, 'Processed Data'!$K$187:$K$191, 'Processed Data'!$K$197:$K$200, 'Processed Data'!$K$229:$K$232, 'Processed Data'!$K$239:$K$242, 'Processed Data'!$K$251:$K$252

Minor Remaining Issues (Modification Not Deemed Necessary)

- The model assumes a constant gender mix at all ages, which is not credible given the higher mortality among men. The impact of this assumption was checked by simulating a cohort of patients, and it was found that this made no substantive difference to the model. No change was made by CDR.
- Given the type of data presented, the initial cirrhosis distribution could have been presented using a Dirichlet distribution, and this would arguably have been more appropriate than the beta distributions used (which are then reweighted). However, the impact of this is expected to be very minor.
- There was inconsistency in the evidence presented for the G3, treatment-naive group, with the standard error of the DCV + SOF SVR rates presented as both 1.8% (manufacturer's pharmacoeconomic evaluation,[3] Table 38) and 2.8% (manufacturer's pharmacoeconomic evaluation,[3] Table 49). From the evidence presented, it appears that only the first of these could be consistent with the model evidence presented and, hence, was used in the reanalysis.

Reanalyses

All models were rerun with the corrected models. A series of reanalyses was suggested and run:

- incorporating SOF price reduction scenarios (20% to 40%), with a threshold analysis additionally run
- incorporating health-management costs from Myers et al. (2014)[14] in place of costs from the CADTH therapeutic review[5]
- incorporating varying discontinuation rates, exploring effects of the same discontinuation rates between DCV and comparator regimens
- assessing effects of alternative health state utilities.

As the intention of several of these analyses is firstly to identify the sensitivity to this issue, results from the DCV + SOF cohort across F0 to F4 — as originally run (assuming a12-week treatment duration) — are presented in some cases.

Sofosbuvir Price-Reduction Scenarios

These comparisons are presented for treatment-naive G3 (SOF as treatment and comparator).

TABLE 13: GENOTYPE 3 F0 TO F3, DACLATASVIR PLUS SOFOSBUVIR VERSUS SOFOSBUVIR PLUS RIBAVIRIN

SOF Price Reduction	Incremental Costs	Incremental QALYs	ICUR
20%	–$21,928	0.06	DCV dominant
30%	–$16,451	0.06	DCV dominant
40%	–$10,971	0.06	DCV dominant

DCV = daclatasvir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOF = sofosbuvir.

DCV + SOF remained dominant for SOF price reductions of 20% to 40%. A threshold analysis showed that a 65% price reduction of SOF would result in an ICUR of DCV + SOF versus SOF + RBV of around $46,000 per QALY, while an SOF discount of 66% leads to an ICUR of $55,000 per QALY for DCV + SOF versus SOF + RBV.

As the cirrhotic (F4) group is not cost-effective, CDR did not consider the effect of reducing the price of SOF further.

Alternative Source for Hepatitis C Management Costs

The disease-specific cost figures from Myers et al. (2014)[14] were analyzed. These figures were in 2013 Canadian dollars and, in order to reflate to 2014 costs, the Canadian Health and Personal Care element of the Consumer Price Index (CPI) was used (in line with the approach taken by Myers et al., 2014[14]) (CPI [2014] at 121.6 and CPI [2013] at 120.5; inflation 2013 to 2014 is 0.9%).

These revised health-management costs are much lower, and the same cost is used for both SVR and the corresponding F0 state. The impact of this change was explored for the G3 treatment-naive case, comparing DCV + SOF versus SOF + RBV (F0 to F4 original case).

TABLE 14: IMPACT OF USING AN ALTERNATIVE SOURCE OF HEPATITIS C MANAGEMENT COSTS

	DCV + SOF Versus SOF + RBV					
	Default Costs			Myers et al. (2014)[14]		
	Cost ($)	QALYs	Cost/QALY ($)	Cost ($)	QALYs	Cost/QALY ($)
Treatment group	$155,675	12.41		$90,324	12.42	
Control group	$188,559	12.35		$123,421	12.35	
Incremental	–$32,884	0.06	**Dominant**	–$33,097	0.06	**Dominant**

DCV = daclatasvir; QALY = quality-adjusted life-year; SOF= sofosbuvir; RBV= ribavirin.

Overall, the use of alternative costs appears to make a difference to the magnitude of costs but has very little impact on incremental costs. In part, this is due to the fact that most patients will still spend most of the time in early years within the non-complication and SVR states. The impact of the change is to decrease the costs for both model groups. This change does not appear to affect the cost-effectiveness acceptability frontier for this comparison, with a 100% chance of cost-effectiveness in both cases.

Alternative Source for Health States Utilities

The health state utilities in the default model were based on the CADTH therapeutic review[5] figures. The utility figures for Chong et al. (2003)[23] are provided as part of the options in the model, and the comparison for the G3 treatment-naive case (DCV + SOF versus SOF + RBV) was rerun with this set of parameters. When this model was rerun, there was a clear drop in the QALYs obtained in both cases, and a small drop in incremental QALYs from using DCV + SOF case. However, DCV + SOF remained dominant. In terms of the cost-effectiveness acceptability curves, the likelihood of cost-effectiveness at $50,000 per QALY was 100% both before and after this change.

Impact of Applying Disutility Associated to Adverse Events

The inclusion or exclusion of disutility associated to adverse events did not seem to significantly impact results.

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