Common Drug Review
Pharmacoeconomic Review Report

July 2016

Drug	Asunaprevir (Sunvepra)
Indication	In combination with other agents for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1 or 4 and compensated liver disease, including cirrhosis.
Listing request	In combination with other agents for the treatment of chronic HCV infection and compensated liver disease (including cirrhosis) for the following regimen: • Daclatasvir + Asunaprevir: Treatment of G1b chronic HCV infection • Daclatasvir + Asunaprevir QUAD THERAPY (with PR): In a similar manner as interferon-based therapies already listed for the treatment of G1 and G4.
Dosage form(s)	100 mg capsule
NOC date	March 9, 2016
Manufacturer	Bristol-Myers Squibb

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
ASV	asunaprevir
BOC	boceprevir
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CPI	consumer price index
DAA	direct-acting antiviral
DB	double-blind
DCV	daclatasvir
DCV + ASV	daclatasvir plus asunaprevir
DCV/ASV + PR	daclatasvir plus asunaprevir and pegylated interferon plus ribavirin
F0	no fibrosis
F1	portal fibrosis with no septa
F2	portal fibrosis with few septa
F3	portal fibrosis with numerous septa
F4	compensated cirrhosis
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
ITT	intention-to-treat population
MAIC	matching-adjusted indirect treatment comparison
MONARCH	MOdelling the NAtural histoRy of Cost-effectiveness of Hepatitis
METAVIR	Meta-analysis of Histological Data in Viral Hepatitis
NMA	network meta-analyses
OMB/PAR/RIT	ombitasvir/paritaprevir/ritonavir
P2aR	pegylated interferon 2a plus ribavirin
P2bR	pegylated interferon 2b plus ribavirin
PR	pegylated interferon plus ribavirin
QALY	quality-adjusted life-year
RBV	ribavirin
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
TEL	telaprevir
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

<table>
<tr><td>Drug Product</td><td>ASV 100 mg as a component of a combination antiviral treatment regimen</td></tr>
<tr><td>Study Question</td><td>• Is the DCV + ASV 24-week regimen a cost-effective option when compared with the standard of care antiviral regimens in CHC patients infected with HCV genotype 1b?
• Is the DCV/ASV + PR 24-week regimen a cost-effective option when compared with the standard of care antiviral regimens in CHC patients infected with HCV genotype 1 and 4?</td></tr>
<tr><td>Type of Economic Evaluation</td><td>Cost-utility analysis</td></tr>
<tr><td>Target Population</td><td>Patients with CHC genotype 1, 1b, or 4 TN or TE, including partial responders, relapsers, and null responders</td></tr>
<tr><td>Treatment</td><td>• DCV 60 mg once daily + ASV 100 mg twice daily for 24 weeks (genotype 1b)
• DCV 60 mg once daily + ASV 100 mg twice daily in combination with PR for 24 weeks (genotype 1 and 4)</td></tr>
<tr><td>Outcome</td><td>QALYs</td></tr>
<tr><td>Comparators</td><td>
<table>
<tr><th>Genotype 1 and 1b</th><th>Genotype 4</th></tr>
<tr><td>SOF + PR 12 weeks
SIM + PR RGT or 48 weeks
TEL + PR RGT or 48 weeks (discontinued)
BOC + PR RGT or 48 weeks
PR 48 weeks</td><td>SOF + PR 12 weeks
(currently not listed on drug plans)
PR 48 weeks</td></tr>
<tr><td colspan="2">Comparisons with the above treatments were not available for all subgroups</td></tr>
</table>
</td></tr>
<tr><td>Perspective</td><td>Ministry of Health</td></tr>
<tr><td>Time Horizon</td><td>Lifetime</td></tr>
<tr><td>Results for Base Case</td><td>
<table>
<tr><td>HCV genotype
Treatment</td><td>Genotype 1 (64%)</td><td>Genotype 1b (23%)</td><td>Genotype 4 (2%)</td></tr>
<tr><td>Comparator</td><td>DCV/ASV + PR 24 weeks ($/QALY)</td><td>DCV + ASV 24 weeks ($/QALY)</td><td>DCV/ASV + PR 24 weeks ($/QALY)</td></tr>
<tr><td>SOF + PR 12 weeks</td><td>NA</td><td>TN: DCV + ASV Dominant</td><td>DCV/ASV + PR Dominant[a]</td></tr>
<tr><td>SIM + PR RGT or 48 weeks</td><td>NA</td><td>TN & TE: DCV + ASV Dominant</td><td>NA</td></tr>
<tr><td>TEL + PR RGT or 48 weeks</td><td>TE: Dominant</td><td>TN & TE: DCV + ASV Dominant</td><td>NA</td></tr>
<tr><td>BOC + PR RGT or 48 weeks</td><td>TE: DCV/ASV + PR Dominant</td><td>TN & TE: DCV + ASV Dominant</td><td>NA</td></tr>
<tr><td>PR 48 weeks</td><td>TE: < $10,000</td><td>TN & TE: < $10,000</td><td>$15,154[a]</td></tr>
</table>
Note: Above, shaded cells represent the manufacturer's listing request; striped cells show comparators that are no longer relevant (discontinued, no longer indicated, or not currently reimbursed by CDR-participating drug plans for that population).
[a] TE patients for DCV/ASV + PR versus TN patients for comparator.
</td></tr>
</table>

Key Limitations	• The manufacturer's model did not allow comparison between ASV-containing regimens in patients with genotype 1b. It is therefore impossible to determine which ASV-containing regimen is the most cost-effective for this patient population. • Lack of comparison with other interferon-free regimens available (for genotype 1 and 1b patients) and no treatment (for all genotypes) does not provide cost-effectiveness estimates for relevant comparators. • Uncertainty regarding comparative SVR rates: the manufacturer used matching-adjusted indirect comparisons (genotype 1 TN, genotype 1b), naive indirect comparisons (genotype 1 TE, genotype 4), and compared TE and TN populations for some of the comparisons (G4). • Errors in the manufacturer's model; in particular, there were issues with mortality in patients with advanced disease, and the characterization of uncertainty in the probabilistic sensitivity analysis.
CDR Estimate(s)	• A series of CDR reanalyses were run. Results of the reanalyses suggest little change in the manufacturer's results. • The lack of comparison with interferon-free regimens makes it difficult to draw relevant conclusion on the cost-effectiveness of ASV-containing regimens in genotype 1 and 1b, given current reimbursement context of interferon-free regimens by CDR-participating drug plans. • In genotype 4 null responders, the cost-effectiveness of ASV-based regimen is likely to be cost-effective versus PR, although the comparison was based on TE patients for DCV/ASV + PR versus TN patients for PR.

ASV = asunaprevir; BOC = boceprevir; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; DCV = daclatasvir; 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.

EXECUTIVE SUMMARY

Background

Asunaprevir (ASV; Sunvepra) is a protease inhibitor, indicated in combination with other drugs for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1 or 4 and compensated liver disease, including cirrhosis. A Notice of Compliance (NOC) for ASV was issued on March 9, 2016. The recommended dose is 100 mg twice daily for 24 weeks.[1] It is available as 100 mg capsules at a confidential price of or $[redacted] per capsule, or $[redacted] for 24 weeks. For patients with genotype 1b, the licensing request is for ASV to be used in combination with daclatasvir (DCV) 60 mg daily for 24 weeks (total cost of treatment course: $[redacted]). For patients with genotype 1 or 4, the licensing request is for ASV is to be used in combination with DCV and pegylated interferon plus ribavirin (PR) for 24 weeks (total cost of treatment course: $[redacted]).

The manufacturer's requested reimbursement varies based on the genotype:

- DCV + ASV 24-week regimen: Treatment of genotype 1b CHC
- DCV/ASV + PR 24-week regimen: In a similar manner as interferon-based therapies already listed for the treatment of genotype 1 and 4.

All analyses assumed that the price of a 24-week course of DCV will be capped at [redacted]; i.e., total cost of DCV will not exceed $[redacted].

In 2015, before a NOC had been received for ASV, the manufacturer submitted a cost-utility analysis over a lifetime horizon (up to 100 years of age) from a Ministry of Health perspective. The pharmacoeconomic model submitted covered both a DCV and sofosbuvir (SOF) regimen, as well as the ASV-containing regimens mentioned above. Following the issue of the NOC in March 2016, the manufacturer confirmed that there are no changes to the pharmacoeconomic model previously filed, and so the previously prepared report is used as the basis for this review by the CADTH Common Drug Review (CDR).

The analysis assesses the cost-effectiveness of two ASV-containing regimens across treatment-naive and/or treatment-experienced subgroups with various genotypes of HCV (genotype 1, 1b, 4).[2] The comparators varied by genotypes and consisted of direct-acting antivirals (DAAs) in combination with PR, including SOF, simeprevir (SIM), telaprevir (TEL), and boceprevir (BOC), SOF and ribavirin (RBV), and PR alone. The submission uses the MOdelling the NAtural histoRy of Cost-effectiveness of Hepatitis (MONARCH) model, which tracks patients through Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis states 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 the case where SVR was obtained following existing compensated cirrhosis.

The manufacturer reported that the following ASV-containing regimens led to an incremental cost-utility ratio (ICUR) below $50,000 per quality-adjusted life-year (QALY) in the following subgroups:

- DCV + ASV for treatment-naive and treatment-experienced patients with HCV genotype 1b
- DCV/ASV + PR for partial responders with HCV genotype 1
- DCV/ASV + PR for a mixed treatment-experienced group (partial and null responders) with HCV genotype 4.

Summary of Identified Limitations and Key Results

Caution should be exercised in concluding that ASV-containing regimens are cost-effective, as the model did not include relevant comparators; specifically, no treatment and other interferon-free regimens, compared with which ASV-containing regimens may or may not turn out to be cost-effective. Efficacy and adverse event data (including discontinuation) were obtained through matching-adjusted indirect comparisons (MAIC) and naive indirect treatment comparisons. Across the MAIC cases (and especially for genotype 1b), the resulting data lack credibility, as figures for the same ASV-containing regimens in the same patients differ by an order of magnitude, simply because the comparator is different. Other limitations included the lack of a relapse and/or reinfection state, as this will overstate the cost-effectiveness of curative treatments.

The manufacturer's models contained errors, and in particular there were issues with mortality in patients with advanced disease. This issue was corrected by CDR reviewers for this report, alongside an additional issue regarding the characterization of uncertainty.

Conclusions

The general issue with the manufacturer's submission was the lack of relevant comparators and available clinical data to allow comparisons across all subgroups (treatment-naive, partial responders, null responders, relapsers). Even when ASV-containing regimens appear to be cost-effective based on CDR reanalyses, they have not been compared against newer alternatives and the presented evidence also often considers only a limited range of existing therapies. Based on available economic model and data, CDR reanalyses suggest that:

For treatment-naive patients, by genotype:

- Genotype 1: The DCV/ASV + PR regimen was not included in the model, so no conclusion can be made for this regimen in this population.
- Genotype 1b: There is some evidence that DCV + ASV is cost-effective against PR, but some caution should be placed on this finding as SOF + PR, SIM + PR, and interferon-free regimens were not included.
- Genotype 4: The DCV/ASV + PR regimen was not included in the model, so no conclusion can be made for this regimen in this population.

For treatment-experienced groups, by genotype:

- Genotype 1: For partial responders, quad therapy (DCV/ASV + PR) is cost-effective compared with PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.
- Genotype 1b: For a number of groups (partial responders, null responders, relapsers), DCV + ASV is cost-effective versus PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.
- Genotype 4: for null responders, quad therapy (DCV/ASV + PR) appears cost-effective against PR, with SOF + RBV dominated (note that none of the CDR-participating drug plans currently reimburse SOF for genotype 4). However, there is a concern that data for quad therapy were based on treatment-experienced patients, while a treatment-naive group provided the comparator treatments.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis based on Version 5 of the MOdelling the NAtural histoRy of Cost-effectiveness of Hepatitis (MONARCH) model. The MONARCH model[3] classifies fibrosis using the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) stage (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 relapse to HCV-positive states does not occur and progression is limited only to the case 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 prior response within experienced treatment) and HCV genotype. There are two distinct regimens involving ASV (DCV + ASV for 24 weeks and DCV plus ASV and pegylated interferon plus ribavirin [PR] for 24 weeks). However, these DCV regimens are not compared among each other in any patient subgroup. Within each patient subgroup, one DCV + ASV regimen is compared with between one and five other treatment regimens containing PR (in isolation, or in combination with BOC, SIM, SOF, and TEL). 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 (ICUR).

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 Antivirals Agents for Chronic Hepatitis C Genotype 1,*[4] which based its figures on Thein et al. (2008),[5] Hsu et al. 2012,[6] Krajden et al. (2010),[7] and Gao et al. (2012),[8] 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. Although the manufacturer's analyses present only pairwise comparisons, it is optimal to consider all treatment options together to identify which treatment option provides a cost-effective option (frontier analysis).

CADTH Common Drug Review (CDR) reviewers attempted to provide such an analysis, where possible. The results from the manufacturer's submission presents a picture in which there appears to be very little uncertainty as to the most cost-effective option at a willingness-to-pay of around $50,000 per QALY. Where 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.

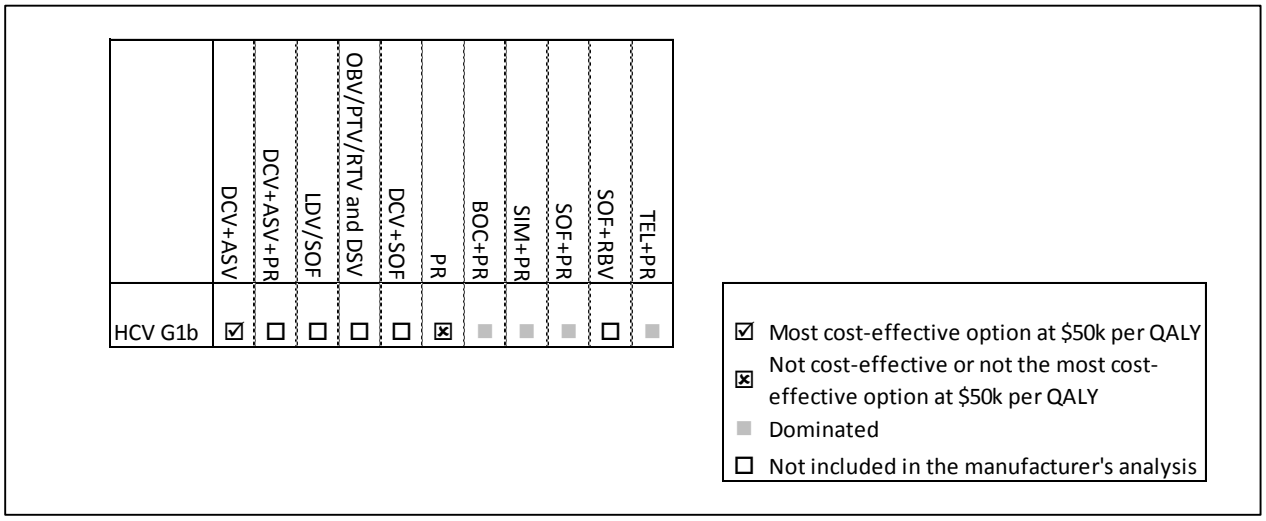
The following figures summarize the apparently optimal choice at threshold values nearing $50,000 per QALY for the treatment-naive and treatment-experienced groups. The figures displayed show (1) subgroups were used, (2) which comparators appeared in each analysis, and (3) whether treatments were dominated, 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

Treatment-Naive Comparisons

For treatment-naive patients, comparisons were presented for genotype 1b (Figure 1).

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



ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; G = genotype; HCV = hepatitis C virus; LDV = ledipasvir; OBV/PTV/RTV and DSV = ombitasvir/ paritaprevir/ritonavir and dasabuvir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life year; RBV = ribavirin;
SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.

For genotype 1b, DCV + ASV is compared against a series of alternatives, with the most relevant comparison finding that it appears the most cost-effective option against PR, all other options being dominated.

Treatment-Experienced Comparisons

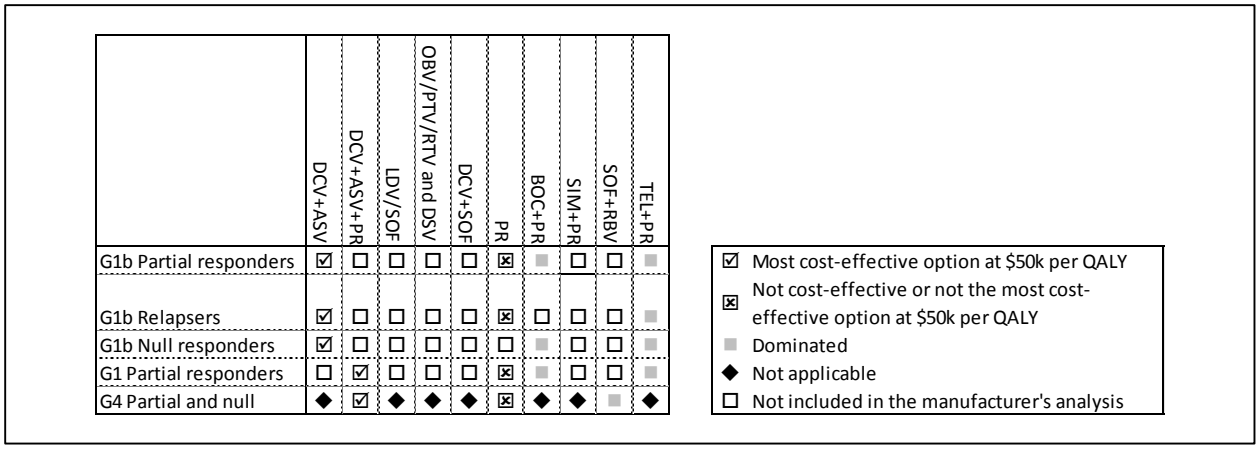
For treatment-experienced patients, comparisons were presented for DCV + ASV regimens in genotype 1, 1b, and 4 (Figure 2).

Evidence for the comparisons came from two trials:

- Hallmark DUAL[9] considered DCV + ASV regimens for genotype 1b patients who were previous non-responders to PR (n = 205), or who were medically ineligible for, previously intolerant of, or ineligible for and intolerant of PR (n = 235)
- Hallmark QUAD[10] considered DCV/ASV + PR for genotype 1 and 4 non-responders to PR.

The vast majority of "treatment-experienced" patients do not appear to have failed treatment with a previous direct-acting antiviral (DAA) regimen.

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



ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; G = genotype; HCV = hepatitis C virus; LDV = ledipasvir; OBV/PTV/RTV and DSV = ombitasvir, paritaprevir, ritonavir and dasabuvir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life year; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.

From Figure 2, it appears to be a consistent finding that the main comparison for cost-effectiveness (of those presented) is between a DCV-containing regimen and PR. The other comparisons presented (using another drug in combination with ribavirin with or without interferon) are dominated wherever they appear. Across these comparisons, the DCV + ASV–containing regimens always appear to be cost-effective within the manufacturer's submission for all treatment-experienced groups considered.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer's submission contains a probabilistic sensitivity analysis (PSA), and explores sensitivity within a series of scenario analyses. These analyses consider both general methodological questions (e.g., appropriate discount rates) and questions specific to this model (e.g., weekly costs of adverse events) together. Unfortunately, the manufacturer's submission does not provide a full account of the results of the sensitivity analyses, beyond giving broad statements suggesting that the results are largely unchanged.

The scenario analyses regarding alternative sources of efficacy information are presented more clearly. In all cases (HCV genotype 1b, treatment-naive; HCV genotype 1 and 4, treatment-experienced patients), 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 remain cost-effective even under slightly more conservative assumptions.

An in-depth scenario analysis was also presented that reduced the prices of SOF, TEL, BOC, and SIM by 30%:

- **DCV + ASV:** For both treatment-naive and treatment-experienced HCV genotype 1b patients, this discount was not sufficient to change the dominance of DCV + ASV over the other regimens considered.
- **DCV/ASV + PR:** For partial responders with HCV genotype 1, the baseline analysis suggested the ASV-containing regimen has an ICUR of more than $9,000 per QALY versus PR, with both the BOC and TEL regimens dominated. While BOC is no longer dominated after the price reduction, neither it nor TEL appear cost-effective in this case. For the mixed treatment-experienced group with HCV genotype 4, the analysis again suggested that the ASV-containing regimen is cost-effective versus PR ($16,000 per QALY), with the TEL regimen dominated; in the revised analysis, the dominance remains.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **There is uncertainty regarding the comparative efficacy and safety of ASV-containing regimens:** Efficacy (SVR) and adverse event rates for the base-case analysis were obtained from matching-adjusted indirect treatment comparisons (MAICs) 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 be used only to indirectly compare two treatments at a time. Consequently, the same DCV + ASV treatment regimen has different SVR rates and different rates of adverse events, depending on the regimen against which it is paired. As a result, it is difficult to treat the evidence presented for DCV + ASV as coherent. Without the ability to treat each ASV-containing regimen as having a coherent evidence base, it is difficult to compare the cost-effectiveness findings for these regimens against other treatment comparators. This makes it very difficult to combine estimates within a single analysis and consider the likelihood that DCV + ASV with or without PR 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 in probabilistic sensitivity analyses, it provides an indication beyond the simple pairwise results reported by the manufacturer.

  There is also some concern about the applicability of some of the data used. For genotype 4 treatment-experienced patients, the populations considered in the comparison were treatment-experienced patients receiving DCV/ASV + PR from Hallmark QUAD (AI447029) and treatment-naive patients receiving PR or SOF + PR (within the manufacturer's benchmarking indirect treatment comparison and NEUTRINO). The implicit assumption is that treatment-naive and treatment-experienced patients receiving PR and SOF + PR will have similar outcomes on these treatments.

- **The submitted model does not include comparisons with other interferon-free regimens currently approved and/or reimbursed for treatment of genotype 1 CHC:** The majority of CDR-participating drug plans reimburse the LDV/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. If interferon-free regimens are considered cost-effective (and a preferred option) against existing treatment regimens (DAA + 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 ASV-containing regimens is incomplete. Even among the comparators that are considered, the manufacturer's model does not allow a clear comparison of all options simultaneously.
- **The submitted model does not allow determination of the most cost-effective DCV + ASV–containing regimen for CHC genotype 1b:** The pharmacoeconomic model did not allow for comparison between ASV-containing regimens in patients with genotype 1b, even though both regimens have been studied in genotype 1b partial responders so an indirect comparison would have been possible. It is therefore impossible to determine which ASV-containing regimen is the most cost-effective for this patient subgroup.
- **Efficacy inputs do not distinguish between subgroups with and without cirrhosis:** The efficacy inputs were not stratified by fibrosis stage. It is assumed that the comparative effectiveness of ASV-containing regimens with other regimens is independent of fibrosis stage, which is likely not the case.
- **The submitted model does not include a watchful waiting or no treatment comparator, even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimens.**
- **The manufacturer's model had several errors and shortcomings:** A revised version of the model was provided by the manufacturer during the CDR review, upon which this report is based. Additional errors were identified in the revised model submitted to CDR and are described below:
    - **Mortality:** A major error in the revised version surrounded the incorporation of mortality into the model. 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 those with more moderate disease.
    - **Reinfection or relapse:** The model assumes that once patients achieve SVR, they are protected from reinfection or 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 SVR12 and SVR24 rates from the clinical trials but there is evidence in the manufacturer's submission that patients do relapse within the trial period, and that relapse or reinfection does occur. Aspinall et al. (2013)[12] 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 have been reinfected.
    - **Probabilistic sensitivity analysis:** A more minor error is the treatment of uncertainty in the model. The probabilistic sensitivity analyses reported by 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.[7] This source was also used in the CADTH Therapeutic Review *Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*.[4] As noted in the CADTH Therapeutic Review report, these costs were not fibrosis-specific; they may overestimate the cost of mild or no fibrosis and underestimate the cost of severe fibrosis.

5. 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.

FIGURE 3: SELECTED ANALYSES

Genotype 1

- Treatment-experienced
  - DCV/ASV + PR vs. BOC + PR (partial responders)
  - DCV/ASV + PR vs. PR (partial responders)

Genotype 1b

- Treatment-naive
  - DCV + ASV vs. SOF + PR
  - DCV + ASV vs. SIM + PR
  - DCV + ASV vs. BOC + PR
  - DCV + ASV vs. PR
- Treatment relapser
  - DCV + ASV relapser vs. SIM + PR
  - DCV + ASV relapser vs. BOC + PR
  - DCV + ASV relapser vs. PR
- Treatment partial responders
  - DCV + ASV relapser vs. SIM + PR
  - DCV + ASV partial responders vs. BOC + PR
  - DCV + ASV partial responders vs. PR

Genotype 4

- Treatment-experienced, DCV/ASV + PR 24 week vs. PR 48 weeks

ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; MAIC = matching-adjusted indirect comparisons; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; vs. = versus.

6. CADTH COMMON DRUG REVIEW REVISED BASE CASE

There were errors in the manufacturer's original submitted model and these necessitated a request to return the model for correction. This was done, although not all errors were fixed and other errors were introduced, mainly regarding mortality and the PSA.

The CDR revised base case included the following changes:

- ICURs are based on the PSA results, in which the number of iterations was increased from 1,000 to 10,000.
- All-cause mortality was incorporated into all health states (including advanced disease states).
- The PSA was modified so that only one random draw is made and all the parameters take this value.

Please refer to APPENDIX , section V: CADTH Common **Drug Review Reanalysis** for further details.

Table 2 provides a summary of the manufacturer's results for these comparisons versus those in the CDR's corrected base-case analyses. Within the CDR analyses, the general conclusions are very similar to the model as provided by the manufacturer, albeit with slightly lower incremental QALYs for the ASV-containing regimens.

TABLE 2: 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 ASV regimen versus comparator**	**Incr. cost**	**Incr. QALYs**	**ICUR ASV regimen versus comparator**
Genotype 1, Treatment-Experienced	BOC + PR	–$4,844	1.40		–$4,760	0.95	
	PR	$23,663	2.57	$9,191 per QALY	$23,702	2.24	$10,588 per QALY
Genotype 1b, Treatment-Naive	SOF + PR	–$25,000	0.08		–$24,994	0.08	
	SIM + PR	–$17,653	0.02		–$17,653	0.02	
	BOC + PR	–$10,637	0.46		–$10,607	0.46	
	PR	$10,567	1.09	$9,695 per QALY	$10,639	1.10	$9,720 per QALY
Genotype 1b, partial responder	BOC + PR	–$19,586	0.84		–$19,583	0.77	
	PR	$9,675	2.14	$4,512 per QALY	$9,704	1.97	$4,928 per QALY
Genotype 1b, relapser	SIM + PR	–$18,050	0.32		–$18,046	0.30	
	BOC + PR	–$19,492	0.60		–$19,479	0.55	
	PR	$9,874	1.65	$5,999 per QALY	$9,902	1.51	$6,558 per QALY
Genotype 4, Treatment-Experienced	PR	$22,569	1.49	$22,567 per QALY	$22,582	1.37	$16,565 per QALY

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

7. ADDITIONAL ANALYSES USING CADTH COMMON DRUG REVIEW REVISED BASE CASE

Of the comparisons presented, a number of comparisons of particular interest across the genotypes (1, 1b, 4) were rerun with the models corrected by CDR. A series of CDR reanalyses were run:

- Incorporating SOF price reduction scenarios (20% to 40%), with additional threshold analysis
- Incorporating health management costs from Myers et al. (2014)[13] in place of costs from Krajden et al. (2010)[7]
- Effects of incorporating adverse event disutilities
- Effects of alternative health state utilities.

Overall, the results of the reanalyses suggest very little change in the manufacturer's results, as represented by (1) whether or not the ASV-containing regimen appeared to dominate alternatives and

(2) the ICUR in the cases where the ASV-containing regimen provided additional health at an additional cost. Further details on these results and individual analyses are presented in APPENDIX

8. ISSUES FOR CONSIDERATION

All analyses assumed that the price of a 24-week course of DCV will be capped at [redacted]; i.e., the total cost of DCV will not exceed $[redacted]. No details were provided by the manufacturer on how this cap will be implemented. Should the cap not be implemented, the course of a 24-week regimen of DCV would be $[redacted], which is more expensive than an eight-week course of LDV/SOF ($44,667) and a 12-week course of ombitasvir/paritaprevir/ritonavir and dasabuvir ($55,860).

Patient Input

Input was received by 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 its low toxicity and lack of drug interactions, ASV is expected to open up treatment to patients who had contraindications to, or who couldn't tolerate, interferon-based treatments. With a cure, they expect that their cirrhosis will reverse, and their risk of end-stage liver disease will be reduced. Some may be able to return to work, and the quality of life of everyone will improve. However, some patients were concerned about side effects — specifically, that RBV might be needed for some HCV sufferers. Several patients noted that they were discouraged from seeking treatment because of the continued presence of RBV in contemporary therapy options. Patients also questioned the place of ASV amid contemporary HCV therapies like SOF and LDV/SOF and suggested it might be designed for more difficult-to-treat populations.

9. CONCLUSIONS

The general issue with the manufacturer's submission was the lack of relevant comparators and available clinical data to allow comparisons across all subgroups (treatment-naive, partial responders, null responders, relapsers). Even when ASV-containing regimens appear to be cost-effective based on CDR reanalyses, they have not been compared against newer alternatives and the presented evidence also often considers only a limited range of existing therapies. Based on available economic model and data, CDR reanalyses suggest the following:

- For treatment-naive patients, by genotype:
  - Genotype 1: The DCV/ASV + PR regimen was not included in the model, so no conclusion can be made for this regimen in this population.
  - Genotype 1b: there is some evidence that DCV + ASV is cost-effective against PR, but some caution should be placed on this finding as SOF + PR, SIM + PR, and interferon-free regimens were not included.
  - Genotype 4: The DCV/ASV + PR regimen was not included in the model, so no conclusion can be made for this regimen in this population.

- For treatment-experienced groups, by genotype:
  - Genotype 1: for partial responders, quad therapy (DCV/ASV + PR) is cost-effective compared with PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.
  - Genotype 1b: For a number of groups (partial responders, null responders, relapsers), DCV + ASV is cost-effective versus PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.

- Genotype 4: For null responders, quad therapy (DCV/ASV + PR) appears cost-effective against PR, with SOF + RBV dominated (note that none of the CDR-participating drug plans currently reimburse SOF for genotype 4). However, there is a concern that data for quad therapy were based on treatment-experienced patients, while a treatment-naive group provided the comparator treatments.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 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 reimbursement prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
DCV (Daklinza) + **ASV (Sunvepra)**	60 mg	Tab	[redacted][a]	60 mg daily	**24 weeks**	[redacted][a]	[redacted]
Genotype 1b	**100 mg**	**Tab**	[redacted][a]	**100 mg twice daily**		[redacted]	
DCV/ASV + PR ***Genotype 1***	**+ 180 mcg / 200 mg**	**Vial/tab**	**407.3900**	**+ PegIFN 180 mcg/week; RBV 800 mg to 1,200 mg/day**		**9,777**	[redacted]
Interferon-free regimens							
DCV (Daklinza) + SOF (Sovaldi)	60 mg	Tab	[redacted][a]	60 mg daily	12 to 24 weeks	[redacted][a]	[redacted] to
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
EBR/GZR (Zepatier)	50 mg/ 100 mg	Tab	717.8571[b]	50 mg/100 mg daily	12 weeks[c]	60,300	60,300
EBR/GZR (Zepatier) + RBV	50 mg/ 100 mg	Tab	717.8571[b]	50 mg/100 mg daily	16 weeks[d]	80,400	83,648 to 86,084
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	800 mg to 1,400 mg daily		3,248 to 5,684	
LDV/SOF (Harvoni)	90 mg/ 400 mg	Tab	797.6190	90 mg/400 mg daily	8 to 24 weeks[e]	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)	44,667 67,000 to 134,000
OMB/PAR/RIT + DAS (Holkira Pak)	12.5 mg/ 75 mg/ 50 mg 250 mg	3 tabs	665.0000[f]	25/150/100 mg OMB/PAR/RIT daily + 250 mg DAS twice daily	12 weeks[g]	55,860	55,860
OMB/PAR/RIT + DAS (Holkira Pak) + RBV	12.5 mg/ 75 mg/ 50 mg 250 mg	Tab	665.0000[f]	As above, plus 1,000 mg to 1,200 mg/day RBV	12 to 24 weeks[g]	55,860 to 111,720	55,860 to 111,720
	200 mg 400 mg 600 mg		0.0001[f]				

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
SOF (Sovaldi) + RBV	400 mg	Tab	654.7619	400 mg daily	24 weeks[h]	110,000	116,090 to 117,308
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		6,090 to 7,308	
SIM (Galexos) + SOF (Sovaldi)	150 mg	Cap	434.5500	150 mg daily	12 to 24 weeks[i]	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
DAAs in combination with peginterferon alfa plus ribavirin therapy							
SOF (Sovaldi) + PR	400 mg	Tab	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg/ 200 mg	Vial/tab	407.3900	PegIFN 180 mcg/week; RBV 1,000 mg to 1,200 mg daily		4,889	
SIM (Galexos) + PR	150 mg	Cap	434.5500	150 mg daily	12 weeks	36,502	46,279 to 56,057
	180 mcg/ 200 mg	Vial/tab	407.3900	PegIFN 180 mcg/week; RBV 800 mg to 1,200 mg/day	24 to 48 weeks[j]	9,777 to 19,555	
BOC (Victrelis) + PR	200 mg	Cap	12.5000	800 mg 3 times daily added after 4 weeks PR	24 to 44 weeks	25,200 to 46,200	37,475 to 67,243
	120 mcg/ 200 mg	Pens/ Caps	876.7800	PegIFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day[h]	28 to 48 weeks	12,275 to 21,043	
BOC/ P2bR (Victrelis Triple)	200 mg/80 mcg/200 mg 200 mg/100 mcg/200 mg 200 mg/ 120 mcg/ 200 mg 200 mg/ 150 mcg/ 200 mg	168 Caps+ 2 Pens+ 56 Caps	2652.55[k] 2652.55[k] 2726.00[k] 2726.00[k]	BOC 800 mg 3 times daily; pegIFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/ day, initiate after 4 weeks Pegetron therapy	24 to 44 weeks[l]	31,831 to 59,972	31,831 to 59,972
Peginterferon alfa plus ribavirin therapy							
Peginterferon alfa-2a + RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or syringe/ 28 Tabs 35 Tabs 42 Tabs	407.3900	PegIFN 180 mcg/week; RBV 1,000 mg to 1,200 mg/day[h]	48 weeks	19,555	19,555

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Peginterferon alfa-2b + RBV (Pegetron)	50 mcg/ 200 mg	2 Vials + 56 Caps	793.4700[k]	PegIFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day	48 weeks	19,043	19,043
	150 mcg/ 200 mg	2 Vials + 84 or 98 Caps	876.7800[k]			21,043	21,043
	80 mcg/ 200 mg 100 mcg/ 200 mg 120 mcg/ 200 mg 150 mcg/ 200 mg	2 Pens / 56 to 98 Caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

ASV = asunaprevir; BOC = boceprevir; CDR = CADTH Common Drug Review; DAA = direct-acting antiviral; DAS = dasabuvir; DCV = daclatasvir; EBR = elbasvir; GZR = grazoprevir; HCV = hepatitis C virus; IFN = interferon; LDV = ledipasvir; mcg = micrograms; OMB = ombitasvir; PAR = paritaprevir; P2bR = pegylated interferon 2b plus ribavirin; pegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RIT = ritonavir; RNA = ribonucleic acid; SIM = simeprevir; SOF = sofosbuvir.

Note: All prices are from the Saskatchewan Drug Plan online formulary (Apr 2016), unless otherwise indicated.

[a] Manufacturer's confidential submitted price. Note that while 24 weeks of DCV therapy would cost $[redacted] per patient, the manufacturer will cap the price paid by plans to that of a [redacted] supply, or $[redacted].

[b] Price from IMS Brogan DeltaPA (April 2016, Association québécoise des pharmaciens propriétaires price). Zepatier is currently under review by CDR for the treatment of HCV genotypes 1, 3, and 4.

[c] Twelve weeks for genotype 1 treatment-naive and treatment-experienced relapsers, as well as for treatment-experienced on-treatment virologic failure in patients with genotype 1b. Eight weeks can be considered in treatment-naive genotype 1b patients without significant fibrosis or cirrhosis.

[d] For genotype 1a patients with treatment-experienced on-treatment virologic failure.

[e] 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 HCV RNA < 6 million IU/mL.

[f] List price is $665 per daily dose. Moderiba brand RBV is reimbursed at 0.0001 per tablet when used by Holkira Pak patients. When not provided free of charge, a 12- to 24-week course of RBV would cost $3,045 to $7,308 per patient.

[g] Twelve 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 pegIFN and RBV.

[h] For treatment-naive and treatment-experienced non-cirrhotic patients with genotype 1 who are ineligible to receive an IFN.

[i] Twelve weeks for treatment-naive, prior relapse patients, or prior non-responders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.

[j] Twenty-four weeks for treatment-naive or prior relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. 48 weeks for treatment-naive or prior relapse patients with cirrhosis and HIV coinfection. Forty-eight weeks for prior non-responders with or without cirrhosis and with or without HIV coinfection.

[k] Ontario Drug Benefit Formulary Exceptional Access Program (Apr 2016).

[l] Treatment duration is response-guided based on viral load.

TABLE 4: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHC GENOTYPE 4

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
DCV (Daklinza) + **ASV (Sunvepra) + PR**	60 mg	Tab	[redacted][a]	60 mg once daily	**24 weeks**	[redacted][a]	[redacted]
	100 mg	**Tab**	[redacted][a]	**100 mg twice daily**		[redacted]	
	180 mcg/ 200 mg	Vial/tab	407.3900	PegIFN 180 mcg/week; RBV 800 mg to 1,200 mg/day		9,777	
Interferon-free regimens[d]							
EBR/GZR (Zepatier)	50 mg/100 mg	Tab	717.8571[b]	50 mg/100 mg once daily	12 weeks[c]	60,300	60,300
EBR/GZR (Zepatier) + RBV	100 mg/50 mg	Tab	717.8571[b]	50 mg/100 mg once daily	16 weeks[d]	80,400	61,915 to 64,351
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	800 mg to 1,400 mg daily		3,248 to 5,684	
OMB/PAR/RIT (Technivie) + RBV	12.5 mg 75 mg 50 mg	Tab	665.0000 per 2 tabs	25 mg/150 mg/ 100 mg once daily	12 weeks[c]	55,860	58,905 to 59,514
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
SIM (Galexos) + SOF (Sovaldi)	150 mg	Cap	434.5500	150 mg daily	12 to 24[e] weeks	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619	400 mg once daily		55,000 to 110,000	
DAAs in combination with peginterferon alfa plus ribavirin therapy							
SOF (sofosbuvir) + PR	400 mg	Tab	654.7619	400 mg once daily	12 weeks	55,000	59,889
	180 mcg/ 200 mg	Vial/tab	407.3900	PegIFN 180 mcg/week; RBV 800 mg to 1,200 mg/day		4,889	
SIM (Galexos) + PR	150 mg	Cap	434.5500	150 mg once daily	12 weeks	36,502	46,279 to 56,057
	180 mcg/ 200 mg	Vial/tab	407.3900	PegIFN 180 mcg/week; RBV 800 mg to 1,200 mg/day	24 to 48 weeks[f]	9,777 to 19,555	
Peginterferon alfa plus ribavirin therapy							
Peginterferon alfa-2a + RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or syringe/ 28 Tabs 35 Tabs 42 Tabs	407.3900	PegIFN 180 mcg/week; RBV 1,000 mg to 1,200 mg/day[g]	48 weeks	19,555	19,172

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Peginterferon alfa-2b + RBV (Pegetron)	50 mcg/200 mg	2 Vials + 56 Caps	793.4700[h]	PegIFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day	48 weeks	19,043	19,043
	150 mcg/ 200 mg	2 Vials + 84 or 98 Caps	876.7800[h]			21,043	21,043
	80 mcg/200 mg 100 mcg/ 200 mg 120 mcg/ 200 mg 150 mcg/ 200 mg	2 Pens / 56 to 98 Caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

ASV = asunaprevir; BOC = boceprevir; CDR = CADTH Common Drug Review; DAA = direct-acting antiviral; DAS = dasabuvir; DCV = daclatasvir; EBR = elbasvir; GZR = grazoprevir; HCV = hepatitis C virus; IFN = interferon; LDV = ledipasvir; mcg = micrograms; OMB = ombitasvir; PAR = paritaprevir; P2bR = pegylated interferon 2b plus ribavirin; pegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RIT = ritonavir; RNA = ribonucleic acid; SIM = simeprevir; SOF = sofosbuvir.

Note: All prices are from the Saskatchewan Drug Plan online formulary (Apr 2016) unless otherwise indicated.

[a] Manufacturer's confidential submitted price. Note that while 24 weeks of DCV therapy would cost $[redacted] per patient, the manufacturer will cap the price paid by plans to that of a [redacted] supply, or $[redacted].

[b] Price from IMS Brogan DeltaPA (April 2016, Association québécoise des pharmaciens propriétaires price). Zepatier is currently under review by CDR for the treatment of HCV Genotypes 1, 3, and 4.

[c] Twelve weeks for genotype 4 treatment-naive and treatment-experienced relapsers.

[d] For genotype 4 patients with treatment-experienced on-treatment virologic failure.

[e] Twelve weeks for treatment-naive, prior relapse patients, or prior non-responders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.

[f] Twenty-four weeks for treatment-naive or prior relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. Forty-eight weeks for treatment-naive or prior relapse patients with cirrhosis and HIV coinfection. Forty-eight weeks for prior non-responders with or without cirrhosis and with or without HIV coinfection.

[g] Forty-eight weeks for genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV coinfection.

[h] Ontario Drug Benefit Formulary, Exceptional Access Program (Apr 2016).

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 regarding the composition of the MAIC were 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 these data was necessary.		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*			

MAIC = matching-adjusted indirect comparison.

TABLE 6: AUTHOR INFORMATION

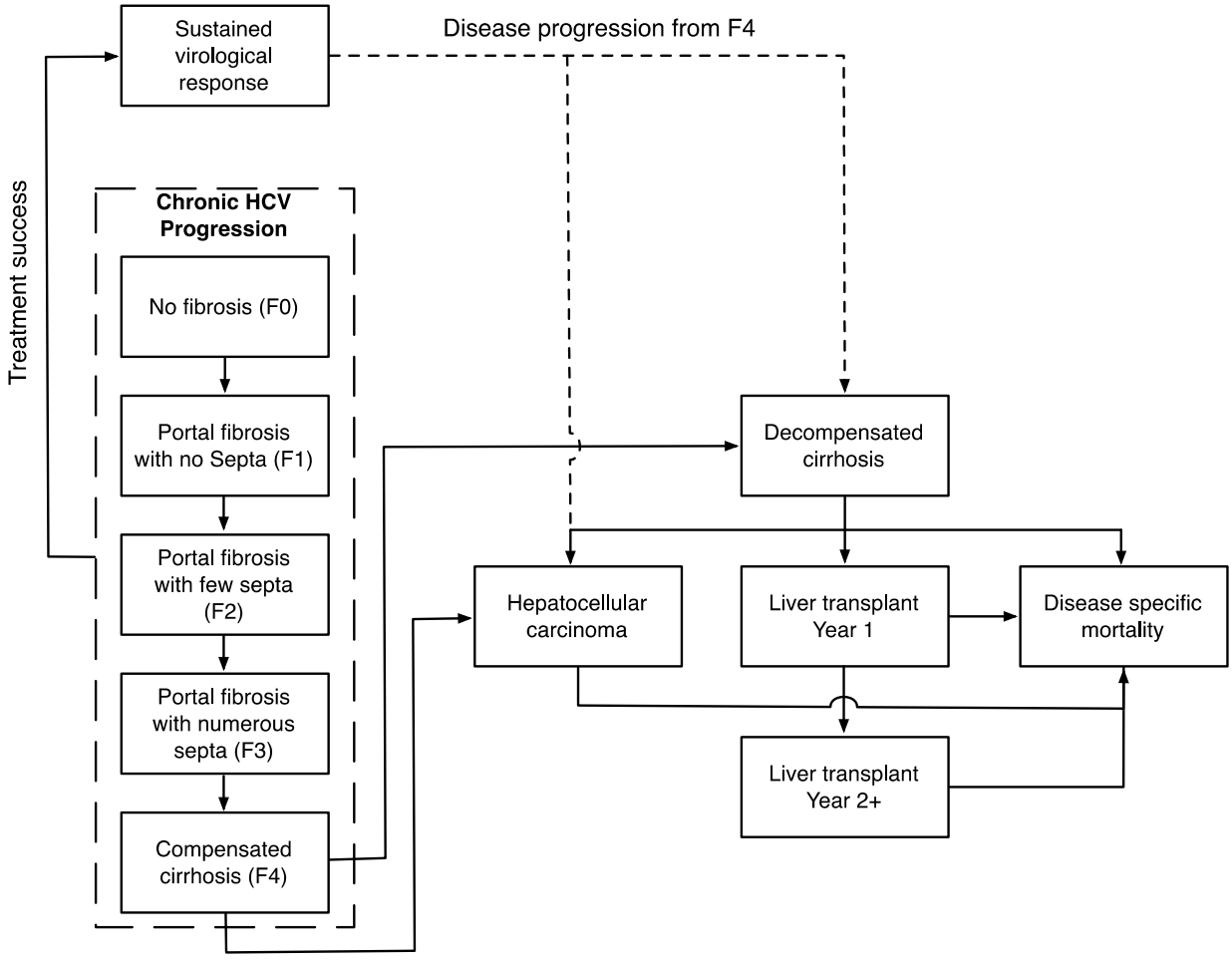
Authors	Affiliations		
	BMS		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The developed model considers a cohort of patients within a Markov simulation, in which 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 using either 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 (Figure 4) is an accurate representation of model structure.

FIGURE 4: MANUFACTURER'S MODEL STRUCTURE



HCV = hepatitis C virus.
Source: Manufacturer's pharmacoeconomic submission.[2]

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 that the MONARCH model has been used previously in three peer-reviewed publications.[14-16] 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 presents a validation analysis in an appendix of the submission, which suggests broad comparability in incremental cost-utility ratios (ICURs) with the CADTH Therapeutic Review[4] and progression for patients entering the model in F0 and F4. Notwithstanding this, there are some issues regarding the calculation of identically distributed items that raise questions as to how accurately the model results may be.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment*
Efficacy	For ASV-containing regimens: • Hallmark DUAL[9] • Hallmark QUAD[10]	The main efficacy data are estimated based on indirect treatment comparisons. (See comment (1).)
Natural history	Transition probabilities based on Thein et al. (2008),[5] as per CADTH Therapeutic Review[4]	Two transition probabilities from decompensated cirrhosis to liver cancer and liver transplant states have been added. Neither appears problematic.
Utilities	Hsu et al. (2012)[6] and McLernon et al. (2008),[17] as used in the CADTH Therapeutic Review.[4] Disutility from adverse events were estimated from Sullivan and Ghushchyan (2006)[18] and Del Rio et al. (2006).[19]	Note that there is no treatment-specific disutility. See comment in Key Assumptions section.
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)	For ASV-containing regimens: • Hallmark DUAL[9] • Hallmark QUAD[10] The data source for the evaluation is based on a secondary analysis of these and other trials.	Further detail on this is given in the Key Assumptions section.
Mortality	Canadian life tables[20]	These figures are not applied consistently within the manufacturer's model.
Costs		
Drug	DeltaPA database. The cost of DCV is capped at [redacted] x weekly cost ($[redacted]) when the duration of treatment is 24 weeks.	
Administration	No administration costs assumed for pegylated interferon.	
AEs	AE costs are assumed to occur only during treatment. Based on Gao et al. (2012)[8] for Anemia and Rash.	Table 61, based on the CADTH Therapeutic Review[4] also includes depression, which is not included in the model.
Health state	Based on Krajden et al. (2010)[7] and the CADTH Therapeutic Review.[4]	Some concerns about appropriateness – see Key Assumptions.

AE = adverse event; ASV = asunaprevir; DCV = daclatasvir.

Comment:

(1) Comparative efficacy and safety via indirect treatment comparisons: For the base case, efficacy (SVR Rates) adverse event and discontinuation rates were obtained from naive indirect comparisons, or matching-adjusted indirect treatment comparison (MAIC), depending on comparisons.

TABLE 8: TREATMENT COMPARISONS IN THE MANUFACTURER'S MODEL

Genotype	Treatment History	ASV-Containing Regimens	Comparators	Type of Comparative Evidence
1	Treatment-experienced	DCV/ASV + PR	PR, SIM + PR, TEL + PR, BOC + PR	Naive ITC
1b	Treatment-naive or treatment-experienced	DCV + ASV	PR, SIM + PR, TEL + PR, BOC + PR, SOF + PR	MAIC (NMA in a sensitivity analysis)
4	Treatment-experienced	DCV/ASV +PR	PR, SOF + PR	Naive ITC

ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect treatment comparison; NMA = network meta-analysis; PR = pegylated interferon plus ribavirin; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

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	This is discussed further in comment (4).
No recurrence or relapse from SVR	Once a patient achieves SVR, it is assumed that they are protected from reinfection 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. For comparison versus trial results, see comment (1) below.
Distribution of initial cirrhosis stages	It is stated that this comes from the CADTH Therapeutic Review,[4] although detail is not given. Table 44 in the economic submission appears to have been copied incorrectly and the data in the model spreadsheet differ slightly from the CADTH Therapeutic Review.
Static transition probabilities	While 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), the submitted model does not appear to do this.
Efficacy figures found via indirect treatment comparisons	MAIC and naive indirect treatment comparisons are assumed to provide a coherent evidence base for ASV-containing regimens. See Data Sources section above.
Costs	
Disease-specific costs classified based "early" and "late" phase cirrhosis	This is discussed in comment (2) below.
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 F0 to F4) are identical. Treatment costs and AE costs are additional to this.
Utilities	
Disutility of treatment relates only to AEs or no treatment-specific disutility	See comment (3) below. 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; ASV = asunaprevir; HCV = hepatitis C virus; MAIC = matching-adjusted indirect comparisons; MONARCH = MOdelling the NAtural histoRy of Cost-effectiveness of Hepatitis; SVR = sustained virologic response.

Comments:

(1) No recurrence or relapse from SVR: For DCV + ASV 24 weeks in genotype 1b, Hallmark DUAL[21] found relapse rates of 3% (treatment-naive), 4% (previous non-responder), and 6% ineligible or intolerant, with another 1% to 2% missing ribonucleic acid (RNA) at post-treatment. 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 after 12 or 24 weeks of treatment (SVR12 or SVR24) — it is likely that this will not include these relapses that occur after treatment cessation, and so the effectiveness of ASV-containing regimens 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.

(2) Disease-specific costs: Disease state–specific costs are based on Krajden et al. (2010),[7] 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.[4]

In Appendix 9, the manufacturer establishes a total cost for HCV patients of $4,557 ("initial stage"), $12,856 ("late stage"), and $43,869 ("pre-death"). These yearly costs correspond to those who have not yet been referred to the health service for liver disease, those who have been referred but who are not yet in the last year of life, and those who are in the final 12 months of life. However, these figures differ from those used in the model, and it is unclear why this is the case.

(3) The CADTH Common Drug Review (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 model presented as above did not include the disutilities of adverse events and as such, there might may be a systematic bias against DCV + ASV regimens.

In addition to the issues regarding adverse events, it is worth noting that substantial 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),[22] the carcinoma state has a utility 0.18 *below* decompensated cirrhosis, while Martin et al. (2012)[23] assigns the same utility (0.45) to both of these states.

(4) Treatment of mortality: The manufacturers have not allowed those in advanced stages of liver disease (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation) to be subject to all-cause mortality. It is stated that this is due to limitations of the modelling approach. It is unclear what these limitations are, or why this should be the case. Other errors were introduced by the manufacturers in their corrected version, and these were corrected by CDR in the reanalysis.

Manufacturer's Results

The manufacturer's submission contains a large number of comparisons and, correspondingly, a large number of results. While 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 (PSA), 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 above with respect to the model, little confidence is placed in the specific values obtained.

Hepatitis C Virus Genotype 1b

Daclatasvir and Asunaprevir in Treatment-Naive Patients

DCV + ASV was estimated to be dominant (higher quality-adjusted life-years [QALYs], cost saving) on average against the regimens combining PR with telaprevir (TEL), boceprevir (BOC), simeprevir (SIM), and sofosbuvir (SOF). In each case, the estimated cost-effectiveness acceptability curve (CEAC) suggests a 100% likelihood of cost-effectiveness.

When compared against pegylated interferon plus ribavirin (PR), the analysis suggests DCV + ASV provides an additional 1.09 QALYs at a cost of nearly $10,567 ($9,695 per QALY), suggesting that DCV will be cost-effective where willingness-to-pay exceeds this figure per QALY.

Daclatasvir and Asunaprevir in Treatment-Experienced Patients

In the comparisons for DCV + ASV patients, the manufacturer's submission suggests DCV + ASV is dominant when compared against PR-based adjunct therapies for partial responders (TEL + PR, BOC + PR), relapsers (TEL + PR, BOC + PR, SIM + PR), and null responders (TEL + PR).

When compared against PR, the manufacturer's submission suggests that DCV + ASV provides highly cost-effective improvements in health for partial responders ($4,512 per QALY) and relapsers ($5,999 per QALY); for null responders, DCV + ASV dominates. In all cases, the DCV + ASV treatment appears to reach 100% likelihood of cost-effectiveness well before a willingness-to-pay of $50,000 per QALY.

Hepatitis C Virus Genotype 1

Daclatasvir and Asunaprevir Plus PR in Treatment-Experienced Patients (Partial Responders Only)

In the comparisons for DCV/ASV + PR patients, the manufacturer's submission suggests the DCV/ASV + PR regimen is dominant when compared against PR-based adjunct therapies for partial responders (TEL + PR, BOC + PR). In the comparison against PR, DCV/ASV + PR is more effective and is cost-effective for willingness-to-pay values exceeding $9,191 per QALY.

As this is a naive indirect treatment comparison, the findings can be confirmed, but are identical to the pairwise cases due to the dominance results.

TABLE 10: MANUFACTURER'S BASE-CASE RESULTS: DACLATASVIR AND ASUNAPREVIR PLUS PR IN TREATMENT-EXPERIENCED PATIENTS (PARTIAL RESPONDERS ONLY)

Decision Option	Incremental Cost-Effectiveness			
	Comparator	**Incr. costs**	**Incr. QALYs**	**ICUR**
PR	BASELINE			
TEL + PR	Dominated			
BOC + PR	Dominated			
DCV/ASV + PR	vs. PR	$21,823	2.38	$9,191 per QALY

ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; ICUR = incremental cost-utility ratio; incr. = increased; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life year; TEL = telaprevir; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission[2]

Hepatitis C Virus Genotype 4

Daclatasvir and Asunaprevir Plus PR in Treatment-Experienced Patients (Population of Partial and Null Responders)

In the comparisons for DCV/ASV + PR patients, the manufacturer's submission suggests the DCV/ASV + PR regimen is dominant when compared against SOF + PR, and cost-effective against PR (ICUR of $15,154 per QALY). At a willingness-to-pay of $50,000 per QALY, the likelihood of DCV + ASV being cost-effective approaches 100%.

However, given that the DCV/ASV + PR data were obtained from treatment-experienced patients, and the PR and SOF + PR data were obtained from treatment-naive patients, nothing can be robustly concluded from this instance of the model.

Manufacturer's Sensitivity Analyses

The sensitivity analyses within the model are primarily (1) the PSAs 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 ribavirin (RBV) (100% price reduction).

There are a large number of different sensitivity analyses, but there is very little reporting of these analyses. In many cases, the cost-effectiveness of the ASV-containing regimens is not substantively affected by the changes made. These are:

- HCV genotype 1b, DCV + ASV for treatment-naive patients
- HCV genotype1b, DCV + ASV for treatment-experienced patients
- HCV genotype 1, DCV/ASV + PR for partial responder patients
- HCV genotype 4, DCV/ASV + PR for treatment-experienced patients.

However, in other cases, there are sufficient changes in the results to potentially change whether or not a treatment might be considered cost-effective. This is generally the case in the scenarios in which treatments do not appear cost-effective but changes to the model reveal at least some circumstances in which they may be. Unfortunately, the reporting of these cases is poor, so that it is not possible to identify generally which cases these are. Although, for example, the manufacturers identify that a non-discounted analysis may make a treatment requiring a large upfront cost appear more attractive, this is hardly surprising. The manufacturer's summary does not distinguish between the scenario changes that affect general methodological questions determined by the CADTH reference case (e.g., discount rates) and those that are specific to the modelling choices. This oversight makes it very difficult to give much weight to the sensitivity analysis presented.

The scenario analyses regarding alternative sources of efficacy information are presented more clearly. In all cases (HCV genotype 1b, treatment-naive; HCV genotype 1 and 4, treatment-experienced patients), the previously cost-effective option remains so after the changes have been made.

A scenario analysis was also presented in depth that reduced the prices of SOF, TEL, BOC, and SIM by 30%. See the earlier section of this report for details.

CADTH Common Drug Review Reanalysis

There were errors in the manufacturer's original submitted model and these necessitated a request to return the model for correction. This was done, although not all errors were fixed and other errors were introduced.

Correcting Treatment of Mortality

The original version of the manufacturer's model contained several flaws with respect to mortality:

- Among those in non-advanced states, the model did not allow for all-cause mortality among those whose disease worsened in the period. This could lead to an unrepresentative cohort in the Markov model, as the only people who can die are those who do not progress — we would expect the model to slightly overstate progression.
- Among those in advanced states, the model did not allow for all-cause mortality to apply.

In the revised version of the manufacturer's model, the former problem is fixed, but the latter remains. The manufacturer suggests that it is too complex to correct this issue. Part of the difficulty here appears to be that the manufacturers have attempted to inappropriately apply liver-specific mortality twice, and then made largely arbitrary modifications to the transition probabilities to allow them to sum to one.

In the version of the model used for CDR reanalyses, the error with the application of liver-specific mortality was resolved, and all-cause mortality was incorporated for those in advanced states. 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 revised model, we observed patients having liver transplants at age 95 and surviving until age 129, when the model ends.

The issues with the manufacturer's model were resolved by CDR. 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 this version of the model, the assumptions surrounding all-cause mortality mean that all patients die at 100 years of age.

Correcting Independent and Identically Distributed Distributions

The MONARCH model will treat figures that might be expected to be "identical" as "identically distributed." This means that in the PSA, the deviates drawn from the "same" distribution will in fact differ. As an example, for the genotype 1 model, 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 reanalysis 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.

Minor Remaining Issues (Modification Not Deemed Necessary)

- In the revised version of the model, an earlier problem with the model using (possibly Scottish) mortality data was removed. This was corrected by the manufacturer, but the model also 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 here.
- 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.

Reanalyses

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

- Incorporating SOF price reduction scenarios (between 20% and 40%), with a threshold analysis additionally run
- Incorporating health management costs from Myers et al. (2014)[13] in place of costs from Krajden et al. [7]
- Incorporating varying discontinuation rates, exploring effects of the same discontinuation rates between DCV and comparator regimens
- Effects of alternative health state utilities.

Sofosbuvir Price Reduction Scenarios

This scenario was relevant for genotype 1b (SOF as a comparator)

TABLE 11: GENOTYPE 1B, DCV + ASV NAIVE MAIC FOR SOF + PR VERSUS SOF + PR NAIVE MAIC

Price Reduction	Incremental Costs	Incremental QALYs	ICUR
0%	–$24,994	0.08	DCV + ASV dominant
20%	–$14,050	0.08	DCV + ASV dominant
30%	–$8,577	0.07	DCV + ASV dominant
40%	–$3,105	0.08	DCV + ASV dominant

ASV = asunaprevir; DCV = daclatasvir; ICUR = incremental cost-utility ratio; MAIC = matching-adjusted indirect comparison; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life year.

At around $50,000 per QALY, the 0.08 difference would mean that this remains cost-effective until we get to an incremental cost of about $4,000. A price reduction of SOF of about 53% would be required to obtain an ICUR nearing $50,000 per QALY.

Alternative Source for Hepatitis C Management Costs

The disease-specific cost figures from Myers et al. (2014)[13] were analyzed. These figures were in 2013 Canadian dollars, and in order to reflate to 2014 costs, the Health Care component of the Canadian Consumer Price Index (CPI)[24] was used (in line with the approach taken by Myers et al., 2014[13]). (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 was used for both SVR and the corresponding F0 state. Overall, the use of alternative costs appeared to make a big difference to the magnitude of costs but had very little impact on incremental costs. In part, this is due to the fact that most patients will still spend most of the time within early years within the non-complication and SVR

states. The impact of the change was to decrease the costs for both arms of the model. This change did not appear to affect the results.

Alternative Source for Health States Utilities

The health state utilities in the default model were based on the CADTH Therapeutic Review[4] figures. The utility figures for Chong et al. (2003)[22] are provided as part of the options in the model. Using the Chong et al. utility values had little impact on the results.

Impact of Applying a Disutility Associated to Adverse Events

In order to assess the impact of adverse events, the "Use AE disutilities" option in the model was checked for the genotype 1b treatment-naive group in the comparison between DCV + ASV and PR. In this case, Table 46 of the manufacturer's submission suggests that 24% of patients treated by PR would be expected to have the Anemia and Rash adverse events. However, when the model was rerun, the drop in utility from including adverse events was only 0.007 QALYs. This suggests that the inclusion or exclusion of adverse events may make only a small difference to the model.

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