# Common Drug Review
## *Pharmacoeconomic Review Report*

**October 2016**

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|---|---|
| **Drug** | Sofosbuvir/Velpatasvir (Epclusa) |
| **Indication** | • For the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis.<br>• In combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis. |
| **Reimbursement request** | As per indication |
| **Dosage form** | Sofosbuvir/Velpatasvir is one tablet of 400 mg/100 mg taken orally |
| **NOC date** | 11 July 2016 |
| **Manufacturer** | Gilead Sciences Canada, Inc. |

**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.

# TABLE OF CONTENTS



**Tables**

**Figures**

# ABBREVIATIONS

| | |
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| **AE** | adverse event |
| **CC** | compensated cirrhosis |
| **CHC** | chronic hepatitis C |
| **DAS** | dasabuvir |
| **DCC** | decompensated cirrhosis |
| **DCV** | daclatasvir |
| **GT1a** | genotype 1a |
| **GT1b** | genotype 1b |
| **GT2** | genotype 2 |
| **GT3** | genotype 3 |
| **GT4** | genotype 4 |
| **GT5** | genotype 5 |
| **GT6** | genotype 6 |
| **EBR/GZR** | elbasvir/grazoprevir |
| **HCC** | hepatocellular carcinoma |
| **ICUR** | incremental cost-utility ratio |
| **LDV/SOF** | ledipasvir/sofosbuvir |
| **LT1** | liver transplantation health state, year 1 |
| **LT2** | liver transplantation health state, subsequent years |
| **NC** | non-cirrhotic |
| **NT** | no treatment |
| **OMB/PAR/r** | ombitasvir/paritaprevir boosted with ritonavir |
| **PR** | pegylated interferon plus ribavirin |
| **PSA** | probabilistic sensitivity analysis |
| **QALY** | quality-adjusted life-year |
| **RBV** | ribavirin |
| **SOF** | sofosbuvir |
| **SVR** | sustained virologic response |
| **TN** | treatment-naive |
| **TE** | treatment-experienced |
| **TEL** | telaprevir |
| **VEL** | velpatasvir |

**TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION**

| Drug Product | SOF/VEL |
|---|---|
| Study Question | (1) Is SOF/VEL cost-effective versus selected comparators for the treatment of chronic HCV infection in adults without cirrhosis or with compensated cirrhosis?<br>(2) Is SOF/VEL + RBV cost-effective versus selected comparators for the treatment of chronic HCV infection in adults with decompensated cirrhosis? |
| Type of Evaluation | Cost-utility analysis |
| Target Population | Patients with chronic HCV infection |
| Treatments | (1) 12 weeks of SOF/VEL for patients with METAVIR scores F0 to F4.<br>(2) 12 weeks of SOF/VEL + RBV for all patients with decompensated cirrhosis. |
| Outcomes | SVR and QALYs |
| Comparators | **GT1**<br>• EBR/GZR (8 weeks [GT1b only], 12 weeks)<br>• EBR/GZR + RBV (16 weeks) (GT1a failure only)<br>• LDV/SOF (8 weeks [low viral load only], 12 weeks, 24 weeks [cirrhotic only])<br>• OMB/PAR/r + DAS (12 weeks) (GT1b only)<br>• OMB/PAR/r + DAS + RBV (12 weeks or 24 weeks [GT1a cirrhotic, prior null response only])<br>• NT<br>**GT2**<br>• SOF + RBV (12 weeks)<br>• PR (24 weeks)<br>• NT<br>**GT3**<br>• EBR/GZR + SOF (12 weeks)<br>• SOF + DCV (12 weeks) (non-cirrhotic only)<br>• SOF + RBV (24 weeks)<br>• PR (24 weeks)<br>• NT<br>**GT4**<br>• OMB/PAR/r + RBV (12 weeks) (non-cirrhotic only)<br>• EBR/GZR (12 weeks)<br>• EBR/GZR + RBV (16 weeks) (treatment-experienced only)<br>• SOF + PR (12 weeks)<br>• NT<br>**GT5/6**<br>• PR (48 weeks)<br>• NT<br>**Decompensated cirrhosis**<br>• LDV/SOF + RBV (12 weeks)<br>• SOF + RBV (48 weeks)<br>• NT |
| Perspective | Canadian public payer |
| Time Horizon | To 80 years of age (30 years) |
| Results for Base Case | For patients without cirrhosis, SOF/VEL would appear to be cost-effective based on manufacturer results for treatment-naive patients with GT2 infection and for treatment-experienced patients with GTs 1a, 1b, 2, or 3 infection.<br>For patients with compensated cirrhosis, SOF/VEL would appear to be cost-effective based on manufacturer results for patients with GTs 1a, 2, and 3 infection. |

| | |
|---|---|
| | Additionally, SOF/ VEL + RBV would appear to be cost-effective based on manufacturer results in all patients with decompensated cirrhosis.<br><br>The manufacturer claims that SOF/VEL is cost-effective in most subgroups of patients with GTs 4 and 5/6. However, this could not be verified by CDR because of significant limitations of the submitted model. |
| **Key Limitations** | • The model is likely to incorrectly report uncertainty in results due to inappropriate treatment of parameter uncertainty, low numbers of model runs, and deterministic results reported as head-to-head results, rather than using an incremental probabilistic analysis.<br>• The only set of incremental analyses the manufacturer provides ("multiple CEACs") cannot be fully interpreted for GTs 4, 5, and 6, as the manufacturer does not generate evidence suitable for forming ICURs between relevant treatment options.<br>• Limited quality clinical evidence and issues in selection of comparators, including (1) effectiveness parameters are drawn from non-comparative trials; (2) sample size of many subgroups with reported 100% SVR rates is low and uncertainty in these estimates is not accounted for appropriately.<br>• Costs of monitoring and for hepatocellular carcinoma states appear unrealistic. |
| **CDR Estimate(s)** | • Many substantive limitations could not be addressed by CDR, and those that could were generally of lesser importance. As a result, CDR has low confidence in the results of the reanalysis.<br>• SOF/VEL does not appear to be cost-effective in treatment-naive, non-cirrhotic patients. SOF/VEL was cost-effective for treatment-experienced non-cirrhotic patients with GTs 1a, 1b, 2, or 3 infection, with ICURs between $8,000 and $12,000 per QALY vs. NT; SOF/VEL was cost-effective in around 40% of model runs in GT1a and GT1b, and 73% and 94% of runs in GT2 and GT3, respectively.<br>• For patients with compensated cirrhosis, SOF/VEL appears to be cost-effective for all patients in GTs 1a, 2, and 3 (ICURs between $6,000 and $27,000 per QALY), although there is a high likelihood (> 60%) that SOF/VEL is not cost-effective for GT1a treatment-naive patients.<br>• Additionally, SOF/VEL + RBV would appear to be cost-effective based on manufacturer results in all patients with decompensated cirrhosis with ICURs of around $30,000 per QALY vs. NT.<br>• No conclusions could be drawn regarding the cost-effectiveness of SOF/VEL for patients with GTs 4 or 5/6 infection due to the limitations of the submitted model. |

DAS = dasabuvir; DCV = daclatasvir; EBR/GZR = elbasvir/grazoprevir; HCV = hepatitis C virus; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; NT = no treatment; OMB/PAR/r = ombitasvir/paritaprevir boosted by ritonavir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF/VEL = sofosbuvir/velpatasvir.

# EXECUTIVE SUMMARY

## Background

Sofosbuvir (SOF)/velpatasvir (VEL) (Epclusa) combines sofosbuvir with velpatasvir, a pan-genomic hepatitis C virus (HCV) nonstructural protein 5A (NS5A) inhibitor. It is formulated as a 12-week, single-tablet regimen for chronic HCV (CHC) infection for patients without cirrhosis or with compensated cirrhosis (Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] F0 to F4), and in conjunction with ribavirin (RBV) for patients with decompensated cirrhosis. The recommended dose is 400 mg/100 mg daily for 12 weeks. The manufacturer submitted a price of $714.29 per pill, or $60,000 for a 12-week course.

The manufacturer's submission employs a Markov cohort model, in which patients are located in health states representing initial METAVIR scores with active CHC infection, sustained virologic response (SVR) states, distal consequences of HCV infection, and death. The manufacturer presents results for subgroups differentiated by genotype, prior treatment exposure, and cirrhosis status (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis). The comparators varied within the 26 subgroups considered and included direct-acting antivirals (DAAs) with and without RBV, pegylated interferon plus ribavirin (PR), and No Treatment.

The manufacturer's results suggest that SOF/VEL is cost-effective for treatment-naive patients with genotype 2 infection and for treatment-experienced patients with genotypes 1a, 1b, 2, or 3 infection. For patients with compensated cirrhosis, SOF/VEL would appear to be cost-effective based on the manufacturer's results for patients with genotypes 1a, 2, or 3 infection, but not G1b. The manufacturer also claims that SOF/VEL is cost-effective in most subgroups of patients with genotypes 4 and 5/6. Additionally, SOF/VEL + RBV would appear to be cost-effective based on manufacturer results in all patients with decompensated cirrhosis.

## Summary of identified limitations and key results

There were a large number of issues identified in the manufacturer's submitted Pharmacoeconomic Report and Excel model, such that little confidence can be placed in the results. Critically, the treatment of uncertainty in the model is inappropriate, with parameters that should be common across SOF/VEL and its comparators within a model run (such as costs and natural history transition probabilities) allowed to differ between the treatments considered, and other uncertain parameters (such as fibrosis distributions) not included in the probabilistic sensitivity analysis at all. The manufacturer's main reported results are based on deterministic results and consider only head-to-head comparisons of SOF/VEL versus a single comparator at a time, rather than considering all comparators together.

There are also issues with the quality of the clinical evidence and the selection of comparators. The effectiveness parameters of the model are drawn from non-comparative trials and very little data are available for a considerable number of the subgroups considered by the manufacturer. Across the 20 subgroups modelled by data from ASTRAL-1, it appears that 60% of the reported SVR rates are based on fewer than 25 patients and all of these report a 100% SVR rate. Another limitation is that the costs assigned to hepatocellular carcinoma states are much higher than in the recent CADTH Therapeutic Review, and high monitoring costs are assumed for patients treated with non-interferon regimens without sufficient justification.

The CADTH Common Drug Review (CDR) requested clarification on several issues with the model, including an inability to generate all the diagrams (i.e., cost-effectiveness acceptability curves [CEACs]) contained in the manufacturer's submission. The manufacturer's response did not fully address the concerns raised. Although CDR was able to determine how the manufacturer-reported CEACs were created, CDR was unable to correct the identified issues with the model sufficiently to allow values to be reported with confidence.

On the basis of the information that has been provided, the CDR reanalyses suggest tentative conclusions that:

For treatment-naive, non-cirrhotic patients:

- SOF/VEL was dominated by ombitasvir/paritaprevir boosted by ritonavir plus dasabuvir (OMB/PAR/r + DAS) in genotype 1a and 1b infection
- While SOF/VEL appears a relevant option, it has an incremental cost-utility ratio (ICUR) above $50,000 per quality-adjusted life-year (QALY) versus PR in genotypes 2 and 3 infection, and hence does not appear to be cost-effective.

For treatment-naive patients with compensated cirrhosis:

- SOF/VEL appears to be cost-effective in genotypes 1a, 2, and 3.
- SOF/VEL has a high ICUR (exceeding $140,000 per QALY) against OMB/PAR/r + DAS + RBV in genotype 1b, and hence does not appear to be cost-effective.

For treatment-experienced patients:

- In genotypes 1a, 2, and 3, SOF/VEL appears to be cost-effective irrespective of cirrhosis status.
- In genotype 1b, SOF/VEL appears to be a cost-effective option for non-cirrhotic patients but is dominated by OMB/PAR/r + DAS + RBV in cirrhotic patients.

For patients with decompensated cirrhosis, SOF/VEL + RBV appears to be cost-effective in both treatment-naive and treatment-experienced patients.

No conclusions could be drawn regarding the cost-effectiveness of SOF/VEL for patients with genotypes 4 or 5/6 infection due to the limitations of the submitted model.

## Conclusions

Due to the unresolved limitations of the submitted economic analysis, caution is advised in interpreting and applying the results of reanalyses in which SOF/VEL appeared to be cost-effective. Given the uncertain validity of results for genotypes 1, 2, and 3 and patients with decompensated cirrhosis, and the inability to reach any conclusions whatsoever regarding genotypes 4 and 5/6, CDR considered that a price premium for SOF/VEL over non-interferon comparator regimens is not justified.

# INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

## 1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis using a Markov cohort model, where patients are located in one of 17 mutually exclusive health states (Figure 2). Ten of these states distinguish outcomes using the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis scores (F0 to F4) and by whether sustained virologic response (SVR) has been achieved. Two further states consider decompensated cirrhosis, and whether or not SVR has been achieved. Three states cover survival in states representing the distal consequences of chronic hepatitis C (CHC) infection, as hepatocellular carcinoma (HCC) and liver transplantation in both the first and then in subsequent years. The remaining two states consider patients who are dead, either from all-cause mortality or disease-specific mortality.

The model structure allows patients to enter the model either as non-cirrhotic (F0 to F3) patients, in compensated cirrhosis (F4), or in decompensated cirrhosis (DCC). The state(s) in which patients enter the model depend upon the particular subgroup being considered.

The manufacturer presents results for 26 separate subgroups. A total of 24 of these subgroups were formed by considering all combinations of genotype (genotypes 1a, 1b, 2, 3, 4, and combined 5/6), prior treatment exposure (treatment-naive [TN] or treatment-experienced [TE]), and cirrhosis status (non-cirrhotic [NC] as F0 to F3, or compensated cirrhosis [CC] as F4). The final two subgroups consider treatment-naive and treatment-experienced patients with DCC.

The manufacturer compares SOF/VEL against a number of approved and funded comparators, as well as SOF/daclatasvir (DCV) for genotype 3 NC, and elbasvir/grazoprevir (EBR/GZR). A number of older treatments were excluded due to perceived obsolescence. The model results include a number of comparators but typically exclude both no treatment and interferon-based regimens, except for genotypes 2 (TN) and 3 (TN), where pegylated interferon plus ribavirin (PR) is included but no treatment is not, and genotypes 5/6, where both PR and No Treatment results are included. The effectiveness parameters used in the model were drawn from non-comparative trials. There was no formal indirect comparison of trials of relevant comparators; instead, naive direct comparisons were conducted by drawing on SVR results from individual trial arms.

Many elements of the model follow the recent CADTH Therapeutic Review closely,[1] including the natural history, utility figures, and some cost figures. Costs were broken down into drug costs, monitoring costs, adverse event costs, and health state–related costs. Monitoring costs were obtained using a large number of discrete cost items; however, there was no clear breakdown in the submitted report for how these costs were computed.

The patient cohort is assumed to have a mean age of 50 years at the start of the model and is followed up to 80 years of age. The perspective of the model is that of the Canadian publicly funded health care system, with a base currency of 2015 Canadian dollars. A 5% discount rate was applied to both costs and consequences.

# 2. MANUFACTURER'S BASE CASE

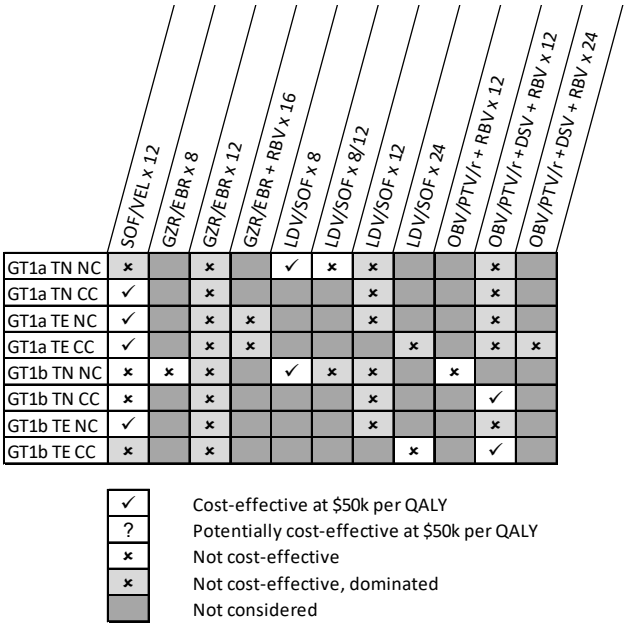
The manufacturer's main results are that SOF/VEL (with or without ribavirin [± RBV]) has demonstrated high SVR rates and is priced in line with other therapies. The manufacturer does not provide a true incremental analysis in its main results but instead provides a large number of analyses comparing SOF/VEL (± RBV) against one other comparator at a time. In contrast, an incremental analysis requires SOF/VEL (± RBV) and all comparators to be compared against each other simultaneously. (This problem is also seen in the main probabilistic sensitivity analysis results.) As such, nothing can be reliably inferred from the manufacturer's main results without further analysis.

In order to do this, the deterministic results from the models were used to construct incremental cost-utility ratios (ICURs), in which each item is compared against increasingly more clinically effective alternatives. In most cases, this was possible with the information provided by the manufacturer. For simplicity, these figures are presented by genotype, covering genotypes 1a and 1b (eight subgroups, Figure 1), then genotypes 2 and 3 (eight subgroups, Figure 2), with the remaining 10 subgroups covering genotypes 4, 5/6, and DCC in a single figure (Figure 3).

**Genotypes 1a and 1b**

For the genotype 1 subgroups, 12 weeks of SOF/VEL is compared against 10 different comparators. Ledipasvir (LDV)/SOF for eight weeks appears to be the most cost-effective option at $50,000 per quality-adjusted life-year (QALY) in the genotype 1a and genotype 1b TN, NC subgroups. SOF/VEL is favoured in all the remaining genotype 1a subgroups, and in each case the manufacturer claims that it dominates every other alternative to which it is compared. For genotype 1b, the only subgroup in which SOF/VEL is favoured is TE NC patients, where the manufacturer again states that it dominates all other alternatives. In genotype 1b TN or TE patients with cirrhosis, ombitasvir/paritaprevir boosted by ritonavir plus dasabuvir (OMB/PAR/r + DAS) + RBV for 12 weeks appears to be the most cost-effective option.

**FIGURE 1: SUMMARY OF COST-EFFECTIVENESS COMPARISONS FOR GENOTYPES 1A AND 1B**

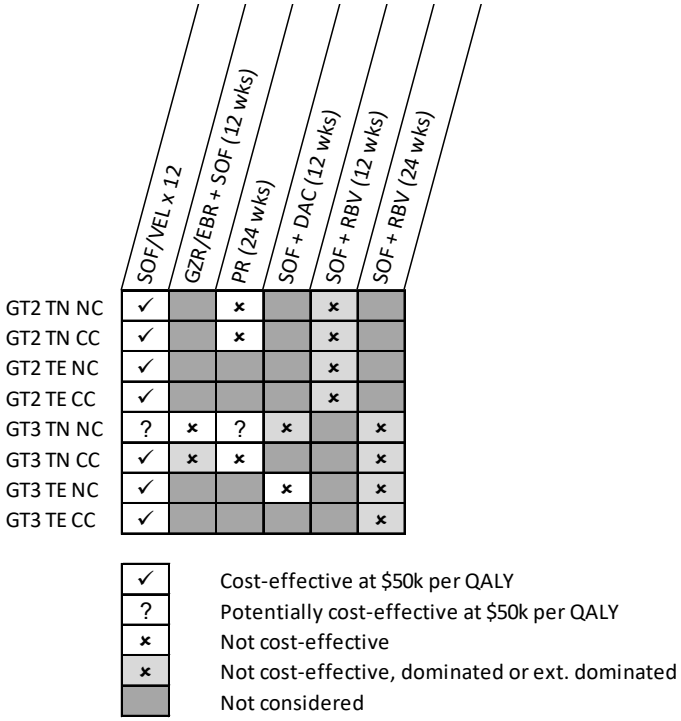



CC = compensated cirrhosis; DSV = dasabuvir; GT = genotype; EBR/GZR = elbasivr/grazoprevir; LDV = ledipasvir; NC = non-cirrhotic; OMB/PTV/r = ombitasvir/paritaprevir boosted with ritonavir; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naive; TE = treatment-experienced; VEL = velpatasvir.

**Genotypes 2 and 3**

The eight subgroups in genotypes 2 and 3 all consider at least one SOF-containing treatment other than SOF/VEL, including SOF + RBV. SOF/VEL appears to be cost-effective in seven of the eight subgroups. In the remaining subgroup (genotype 3, TN, NC patients), its cost-effectiveness is questionable. Here, PR for 24 weeks appears cost-effective at up to approximately $59,000 per QALY, with SOF/VEL cost-effective above this level.

**FIGURE 2: SUMMARY OF COST-EFFECTIVENESS COMPARISONS FOR GENOTYPES 2 AND 3**



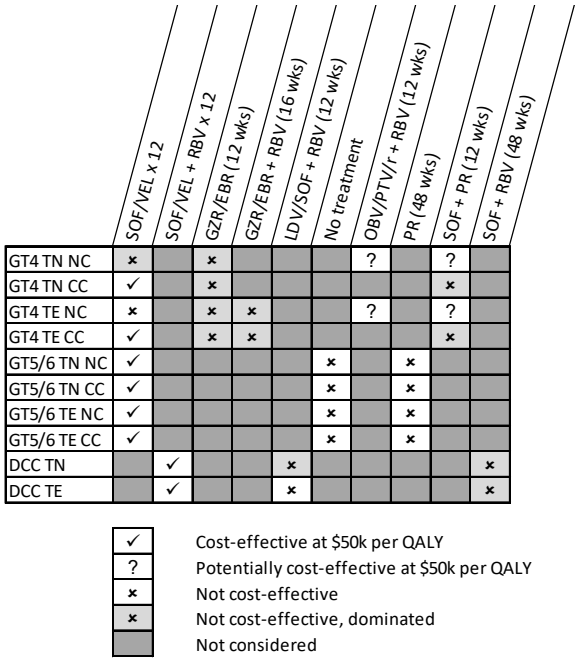

CC = compensated cirrhosis; DCV = daclatasvir; GT = genotype; EBR/GZR = elbasivr/grazoprevir; NC = non-cirrhotic; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naive; TE = treatment-experienced; VEL = velpatasvir.

**Genotypes 4, 5/6, and decompensated cirrhosis**

For patients with genotype 4 infection, SOF/VEL appears cost-effective for patients with cirrhosis, regardless of treatment experience, but not in patients without cirrhosis. It is not possible to identify which treatments are cost-effective in the latter case because of limitations in the precision of the results presented by the manufacturer. However, in neither TN nor TE patients without cirrhosis does SOF/VEL appear cost-effective at $50,000 per QALY.

For patients with genotype 5 or 6 infection, SOF/VEL appears cost-effective in all cases when compared with No Treatment or PR. Likewise, the manufacturer's model suggests that SOF/VEL + RBV is cost-effective for patients with DCC regardless of treatment experience, compared with LDV/SOF + RBV for 12 weeks or SOF + RBV for 24 weeks.

**FIGURE 3: SUMMARY OF COST-EFFECTIVENESS COMPARISONS FOR GENOTYPES 4, 5/6, AND DECOMPENSATED CIRRHOSIS**




CC = compensated cirrhosis; DCC = decompensated cirrhosis; GT = genotype; EBR/GZR = elbasivr/grazoprevir; LDV = ledipasvir; NC = non-cirrhotic; OMB/PTV/ = ombitasvir/ paritaprevir/ boosted with ritonavir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naive; TE = treatment-experienced; VEL = velpatasvir.

# 3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

### Deterministic sensitivity analyses

The deterministic sensitivity analyses reported by the manufacturer examined:

1. Separately varying SVR rates for SOF/VEL and comparators over observed 95% confidence intervals (CIs)
2. Separately varying adverse event rates for SOF/VEL and comparators over observed 95% CIs
3. Varying health state costs by ± 25%
4. Varying health state utilities by ± 25%
5. Varying transition probabilities over observed 95% CIs
6. Varying background mortality rates by ± 25%
7. Applying a discount rate of 0 and 3%.

Given the difficulties in interpreting the manufacturer's results as they are presented, there is little that can be interpreted from the manufacturer's sensitivity analyses. The manufacturer uses tornado diagrams, which limit consideration of uncertainty only to those cases where baseline results did not suggest that either the SOF/VEL or the comparator treatments dominate. The manufacturer does not provide a commentary on the tornado diagrams presented, except to note that results are most sensitive to SVR rates specific to each treatment and health state costs for the initial states.

### Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) presented in the manufacturer's report applied beta and gamma distributions to "key variables"; i.e., utility values, utility decrements due to treatment, and the utility increment due to SVR. Health state costs were also varied, but not drug costs, monitoring costs, or adverse event costs. Transition probabilities were also modified using beta distributions (although Dirichlet distributions are more appropriate where more than two outcomes can occur from a single state).

Due to the limitations of the manufacturer's analysis (presented below), it is difficult to infer much from the results provided, especially where only head-to-head comparisons between SOF/VEL and one other comparator are presented. The manufacturer also provides limited "multiple cost-effectiveness acceptability curves (CEACs)" comparing results across different comparators, although these could not always be verified or interpreted by the CADTH Common Drug Review (CDR) due to their limitations (presented below).

# 4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified a significant number of major limitations with the submitted analyses. Unfortunately, a number of the problems are sufficiently fundamental to the analysis that they could not be remedied without a complete rebuild of the model, which was beyond the scope of the evaluation.

### Selection of comparators and presentation of results

The manufacturer claims that the comparators for an economic evaluation should be the most common and/or least expensive alternatives that are superior to placebo. This statement ignores the possibility of considering No Treatment as an option within a decision, which can be important when there is a possibility of extended dominance between options. It is also important for similar reasons to consider options that are clinically poorer versus a current standard of care. It is worth noting also that the CADTH Therapeutic Review included PR in all genotype 1 and 3 analyses and in all treatment-naive genotype 2 and 4 analyses.[1] The exclusion of this treatment option in the manufacturer's analysis for these genotypes is not sufficiently justified.

None of the manufacturer's main results present an incremental case in which all items are considered together; rather, SOF/VEL is compared with other treatments in a pairwise manner. In Appendix 3 of the Pharmacoeconomic Evaluation Report, the manufacturer provides CEACs that appear to compare multiple options against each other. However, there are no summary tables that allow the results of these diagrams to be interpreted in terms of ICURs, or which can reliably allow the most cost-effective options to be identified. Cost-effectiveness frontiers, which would also allow this, are not provided. Within the submitted Excel model, the functionality to create frontier diagrams is flawed, as the probabilities that options are cost-effective sum to more than 100% in some cases.

Within the CEAC diagrams that can be constructed by the Excel model provided, there are multiple issues. Most importantly, the manufacturer's user guide and subsequent running of the Excel model reveal several instances in which the submitted model appears to differ from the model used to construct the results contained in the manufacturer's submitted report:

- **The Excel model provides a No Treatment option across all subgroups.** In the report, the manufacturer reports a No Treatment option only for genotypes 5/6. In the Excel model provided, No Treatment results are provided in all cases.
- **There is a single, combined model for genotype 4/5/6.** The manufacturer's (deterministic) results for genotypes 4 and 5/6 appear to be identical for SOF/VEL across all four subgroups (i.e., TN NC, TN CC, TE NC, TE CC), and differ only in the selection of comparators. There needed to be separate options to generate results for genotypes 4 and 5/6, based on the clinical data available for each genotype.
- **The genotype 4/5/6 model has no options to identify cirrhotic and non-cirrhotic subgroups or different comparators.** As with the genotype 3 model, the genotype 4/5/6 model has separate forms for treatment-experienced and treatment-naive patients, but lacks much of the functionality necessary to produce the "multiple CEAC" diagrams in the manufacturer's report. When the model is run for cirrhotic and non-cirrhotic subgroups, the only treatments considered are SOF/VEL versus No Treatment. This means that none of the two to four relevant active comparators for genotype 4 subgroups presented by the manufacturer in the main model are considered in generating the CEACs, and only one of two relevant comparators is considered in generating the CEACs for genotype 5/6. It appears that a different macro in the model may generate the manufacturer-reported "multiple CEACs" consisting of all comparators included in the main analysis. However,

these figures are difficult to interpret as they do not identify expected costs or QALYs, and hence do not allow ICURs to be estimated.

- Examples of differences between the results obtained from the submitted model and those provided in the manufacturer's report are listed in APPENDIX .

### Parameter issues

- **The effectiveness parameters used in the model are drawn from non-comparative trials.** The SVR rates used in the model for SOF/VEL are taken from the active arms of the relevant trials.[2-4] It was not possible for CDR to confirm the degree to which the patient populations were clinically comparable, and therefore the degree to which estimates of differential effectiveness used in the model accurately capture the magnitude of the incremental benefit of SOF/VEL.

  There was no formal indirect treatment comparison provided. Instead, naive direct comparisons were conducted from pivotal clinical trials. In many cases, the manufacturer claims a 100% SVR rate from its own trials of SOF/VEL, without clearly indicating the number of patients comprising the analysis. While ASTRAL-1 provided data on patients who received SOF/VEL (n = 624), this trial provides data for 20 distinct subgroups (covering genotypes 1a, 1b, 2, 4, 5/6), and appears to provide the only data available for 16 of the modelled subgroups. The manufacturer subsequently provided disaggregated SVR results for SOF/VEL from ASTRAL-1 (Table 2), although this was received sufficiently late in the review process that it was not possible to use these data to modify the submitted model.

**TABLE 2: DISAGGREGATED SUSTAINED VIROLOGIC RESPONSE RATES FROM ASTRAL-1 USED IN THE MANUFACTURER'S MODEL**

| | GT1a | GT1b | GT2 | GT4 | GT5/6 |
|---|---|---|---|---|---|
| **TN NC** | 107/111 | 76/76 | 72/72 | 56/56 | 53/54 |
| **TN CC** | 21/21 | 10/10 | 6/6 | 8/8 | 7/7 |
| **TE NC** | 50/50 | 18/18 | 21/21 | 33/33 | 10/10 |
| **TE CC** | 28/28 | 13/14 | 4/4 | 19/19 | 4/4 |

CC = compensated cirrhosis; GT = genotype; NC = non-cirrhotic; TE = treatment-experienced; TN = treatment-naive.

Within the model, assumption of 100% SVR from small sample sizes can be problematic when no allowance is made for uncertainty. Across the 20 different subgroups in which these data are used, only eight (40%) have a sample size above 25, where the central limit theorem may give some confidence that the mean value is representative of the population.

Using these data as reported, the manufacturer treats the SVR for genotype 5/6 TE patients with CC as 100%, based on only four patients (with no uncertainty) but the SVR for genotype 5/6 TN NC patients as 98%, based on 54 patients (with uncertainty). With no allowance for sample size, the former subgroup is effectively considered to provide stronger clinical evidence of efficacy than the latter. However, appropriate allowance for the small sample size (e.g., by treating an "extra" patient as equally likely to be a success or failure) would have provided more credible parameters and served to highlight that the clinical evidence is stronger for the latter subgroup.

- **Starting probabilities for fibrosis states are not varied.** This is potentially an important source of uncertainty in the model, especially for less common genotypes. However, this probability is not modified in the model.

- **Monitoring costs do not appear to be justified.** There was no clear breakdown in the manufacturer's submitted report for how monitoring costs were computed, and the figures appear large in some cases. Given the magnitude of many of the monitoring costs, a clear explanation of what they represent and why they are justified was anticipated. For the $7,582 monitoring cost used for 48-week non-interferon treatments, it appears that a total of 24 separate outpatient visits were assumed at a cost of $157 each (so $3,768). This is potentially the most cost-intensive type of visit considered in the model, despite some of these indicated as basic checks. The unit costs for "partial assessments" (at $38.05 rather than $157 per visit) would seem to be more appropriate for these types of visits. This is not the only case of concern, as there are also some odd inclusions in the model, such as pregnancy tests in assessment appointments for patients (both men and women) at least 50 years of age. In contrast to the costs assumed in the manufacturer's model, the CADTH Therapeutic Review did not include costs for monitoring beyond those already counted within the general health state costs.[1]
- **Treatment of HCC costs is inconsistent with the CADTH Therapeutic Review.** The CADTH review states that the "late phase" begins with a diagnosis of DCC or HCC, or both, and has an annual cost of $14,597. In the manufacturer's model, the $14,597 value is used for the DCC state but a different and higher figure of $45,207 is used for the HCC state.
- **No disutilities for adverse events.** Utility data were taken from a variety of studies but were broadly consistent with the CADTH Therapeutic Review. In contrast to the CADTH Therapeutic Review, the manufacturer did not assign a disutility to adverse events, including anemia. Given that SOF/VEL + RBV is associated with some of the highest adverse events within the data, this may be expected to cause bias in some results. The Therapeutic Review assigned a one-time loss of 0.03 QALYs for anemia, 0.0625 QALYs for depression, and 0.0213 QALYs for rash.[1]

**Methodological issues regarding the probabilistic sensitivity analysis**

- **Probabilistic sensitivity analysis is flawed:** Within a PSA, values are drawn for the uncertain parameters — including those affecting more than comparator in the model. It is important that these "common" parameters are used consistently across cases. However, in the model, some parameters, including the costs and utilities attached to different states and the transition probabilities representing natural history, appear to be redrawn separately for SOF/VEL and each comparator. It therefore appears that the sensitivity analyses will incorrectly specify uncertainty around the costs and benefits of options when taken together.
- **Insufficient number of simulations:** The PSA uses 1,000 simulations. When sampling from probability distributions in order to estimate the mean values for costs and outcomes, it is important to run a sufficient number of simulations to ensure that all possible combinations of values on the input distributions are sampled sufficiently frequently that additional simulations will not affect the expected values or the standard errors of the output (costs and QALYs) distributions. Generally, the greater the uncertainty in the input distributions, the larger the number of simulations that will be required to achieve the desired stability. Experience and convention indicates that in excess of 5,000 simulations are likely to be required to achieve stability in most cost-effectiveness models. When fewer simulations are employed, it is the responsibility of the analyst to provide evidence that the output distributions have stabilized. Running a probabilistic analysis with only 1,000 simulations without providing evidence on the stability of the output distributions compared with a higher number of simulations is both unusual and a reason to be highly cautious about accepting the results of the associated probabilistic analysis.
- **No or limited incremental analysis:** Both the deterministic and main PSAs provided are flawed, in that neither presents a true incremental analysis of all options considered against all other options considered. Instead it provides only a comparison of SOF/VEL against each other option in turn,

which is of limited usefulness. The only place where an incremental analysis is presented is where several options are considered simultaneously in the "multiple CEACs", although the issues identified earlier in terms of the Excel model provided to CDR means that CDR cannot interpret these diagrams.

# 5. CADTH COMMON DRUG REVIEW ANALYSES

Many of the concerns detailed above could not be addressed, as they are driven by structural problems with the model, model coding, or fundamental limitations of the evidence base. CDR requested clarification from the manufacturer regarding the lack of specific models for genotypes 4 and 5/6, and the very limited number of comparators within the genotype 4/5/6 model when generating CEACs. The manufacturer's response did not alleviate CDR's concerns.[5]

CDR modified the costs for the HCC state to correspond to the CADTH Therapeutic Review in all cases. With respect to monitoring costs, an initial outpatient visit with a consultant was retained in all cases along with any week 48 outpatient visits, but the following changes were made:

- Monitoring costs identified as "detailed" were changed from a consultant visit ($157) to a medical specific assessment ($79.85).
- Other monitoring costs during active treatment, including "basic checks" and "supplementary monitoring" for 48-week treatments, were changed from a consultant visit ($157) to a partial assessment ($38.05).

CDR also considered providing models incorporating disutilities for adverse events. As SOF/VEL + RBV has some of the highest adverse events within the data, omission of adverse event disutilities may be expected to cause bias in some results. There was no clear place to make such a change in the model, and so the likely impact of this omission was instead considered. In contrast to the manufacturer's model, the CADTH Therapeutic Review assigned a one-time utility loss of 0.03 QALYs for anemia, 0.0625 QALYs for depression, and 0.0213 QALYs for rash. It was estimated that the maximum QALY loss in any arm was only likely to be around 0.02 QALYs (i.e., a net monetary value of $1,000 at $50,000 per QALY); this was judged to be unlikely to substantively change results.

Many of the methodological concerns and issues regarding the selection of comparators could not be resolved by CDR. However, CDR did modify the manufacturer's model to allow a higher number of simulations (to 5,000) in order to provide greater confidence that the means and standard errors of the output distributions were stable.

CDR reran all probabilistic sensitivity analyses available in the manufacturer's model. In general, the results from this analysis were similar to those in the manufacturer's report, although the changes made to the model and the use of No Treatment options within these subgroups led to slight modifications in the results — in particular for TN genotype 2 NC patients. The manufacturer's model could not be verified for genotypes 4 and 5/6, as it does not consider the same comparators as the manufacturer's report. For these subgroups, results are not reported here but are included in the Appendices to this report.

If the manufacturer's model (with modifications) can be relied upon, then SOF/VEL appears to be cost-effective on the basis of the manufacturer's model in a majority of subgroups where results are available.

**Patients without cirrhosis**

For TE patients with genotypes 1a, 1b, 2, or 3 infection without cirrhosis, cost-effectiveness came down to a comparison between SOF/VEL and No Treatment, with other comparators either dominated or extendedly dominated. In these cases, the ICURs obtained were between $8,000 and $12,000 per QALY. While appearing optimal based on the limited evidence available, the likelihood that SOF/VEL is cost-effective at $50,000 per QALY is only around 40% for genotypes 1a and 1b, but much higher (73%, 94%) in genotypes 2 and 3.

In TN patients with genotypes 1a, 1b, 2, or 3 infection without cirrhosis, SOF/VEL does not appear to be cost-effective: Across genotypes, SOF/VEL was dominated in genotypes 1a and 1b, and was cost-effective only at thresholds of approximately $119,000 and $60,000 per QALY in genotypes 2 and 3, respectively.

**Patients with compensated cirrhosis**

SOF/VEL would appear to be cost-effective for all patients with genotype 1a (around $6,000 per QALY versus [vs.] No Treatment), genotype 2 ($27,000 per QALY vs. PR for TN, $6,000 per QALY vs. No Treatment for TE) and genotype 3 ($11,000 per QALY vs. SOF + DCV for TN, $8,000 vs. NT for TE) infection. The likelihood of SOF/VEL being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained was 39% in TN genotype 1a but higher in other subgroups (66% for genotype 2 TN and more than 95% in genotype 2 TE and genotype 3 TN and TE).

In contrast, SOF/VEL does not appear to be cost-effective against OMB/PAR/r + DAS + RBV x 12 for genotype 1b, being dominated for TE patients and having an ICUR of $143,000 for TN patients.

**Patients with decompensated cirrhosis**

SOF/VEL + RBV would appear to be cost-effective based on manufacturer results in all patients with DCC. In these cases, the comparators other than No Treatment are either dominated or extendedly dominated, with ICURs for SOF/VEL of $32,000 and $31,000 per QALY for TN (65% likelihood of cost-effectiveness) and TE patients (84% likelihood of cost-effectiveness), respectively.

While the manufacturer's analyses suggest that SOF/VEL is the most cost-effective option at $50,000 per QALY in many cases, there remains a significant likelihood that SOF/VEL will not turn out to be the most cost-effective treatment option. In part, this is due to serious flaws in the PSAs provided by the manufacturer. Due to the limitations of the model, there is limited confidence in the conclusions that can be obtained from it.

**TABLE 3: SUMMARY OF REANALYZED MANUFACTURER MODELS**

| Subgroup | | | SOF/VEL Cost-Effective Within the Following Threshold Ranges | Prob. SOF/VEL Is CE at $50k per QALY |
|---|---|---|---|---|
| Genotype | Prior Exposure | Cirrhosis Status | | |
| 1a | TN | NC | DOMINATED | 13% |
| 1a | TN | CC | >$6,300 per QALY | 39% |
| 1a | TE | NC | >$12,195 per QALY | 39% |
| 1a | TE | CC | >$5,883 per QALY | 58% |
| 1b | TN | NC | DOMINATED | 5% |
| 1b | TN | CC | >$143,155 per QALY | 28% |
| 1b | TE | NC | >$12,126 per QALY | 40% |
| 1b | TE | CC | DOMINATED | 31% |
| 2 | TN | NC | >$119,185 per QALY | 4% |
| 2 | TN | CC | >$27,364 per QALY | 66% |
| 2 | TE | NC | >$12,196 per QALY | 73% |
| 2 | TE | CC | >$6,000 per QALY | 97% |
| 3 | TN | NC | > $60,037 per QALY & < $13,000,183 per QALY | 32% |
| 3 | TN | CC | >$10,949 per QALY | 97% |
| 3 | TE | NC | > $8,803 per QALY & < $370,855 per QALY | 94% |
| 3 | TE | CC | > $7,680 per QALY | 100% |
| DCC | TN | - | > $32,315 per QALY | 65% |
| DCC | TE | - | > $30,828 per QALY | 84% |

CC = compensated cirrhosis; CE = cost-effective; DCC = decompensated cirrhosis; NC = non-cirrhotic; QALY = quality-adjusted life-year; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive; VEL = velpatasvir.
Note: Shaded rows indicate cases where SOF/VEL is not optimal at $50,000 per QALY.

# 6. PATIENT INPUT

According to patient group input received by CDR for this submission, symptoms of CHC infection vary widely, with some patients having few or no symptoms, and others experiencing fatigue; abdominal, muscle, or joint pain; poor circulation; constipation; diarrhea; nausea; headaches; loss of appetite; sensitivity to light or food; psoriasis; peripheral neuropathy; osteopenia; disrupted sleep; and jaundice. In some patients, the disease affects cognitive function and memory. Fatigue and other symptoms may be severe and can limit patients' ability to work, care for family members, and maintain friendships. The utilities applied in the submitted model likely capture the impact of such symptoms on quality of life to some extent, but may not be reflective of the full spectrum of symptom severity experienced by real-world patients.

Spouses and caregivers for patients with CHC infection are faced with a substantial burden, as the symptoms of CHC infection can leave the patient dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children. The submitted model reflects only costs to the health care system and clinical effects experienced by the patient. While this is appropriate for an analysis conducted from the payer perspective, potential benefits of more effective, less cumbersome, and better-tolerated therapies such as improved productivity or reduced caregiver stress are not captured.

The adverse effects caused by older regimens for CHC infection involving PR were described by patient groups as severe and debilitating; these included extreme fatigue, anemia, depression, anxiety, mood swings, rashes, insomnia, cognitive impairment, irritability, memory loss, headaches, hearing loss, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. The submitted analysis did not incorporate disutilities due to adverse effects, which may have slightly biased estimates in some instances.

Patient group input also described the added challenges faced by patients with HIV and HCV coinfection, particularly with respect to more rapid progression of liver disease and the need to manage potential drug interactions between anti-HIV and anti-HCV medications. The submitted model did not permit estimation of the cost-effectiveness of SOF/VEL in patients coinfected with HIV.

Regimen complexity was described by patient groups as a potential barrier to effective treatment of CHC infection, particularly in relation to treatment adherence. The submitted model was based on SVR rates observed in clinical trials, which may not necessarily reflect real-world effectiveness. To the extent that SOF/VEL, which requires administration of a single tablet daily, is associated with improved adherence (and, consequently, higher SVR rates) than more complex regimens, it may be more cost-effective than suggested by the results of the submitted cost-effectiveness analysis.

# 7. CONCLUSIONS

CDR identified a series of significant concerns regarding the quality of the manufacturer's submission, including use of inappropriate methods (e.g., lack of incremental analyses, flawed approach to PSA), inadequate transparency and clarity in reported methods, and apparent differences between the model used for the manufacturer's report and the model provided to CDR. Although CDR attempted to address what limitations it could, there remain many outstanding points of concern and little confidence is placed in the conclusions. Therefore, caution is advised in interpreting and applying the results of reanalyses in which SOF/VEL appeared to be cost-effective. In light of the significant uncertainties associated with the cost-effectiveness analysis, CDR considered that a price premium for SOF/VEL over non-interferon comparator regimens is not justified.

# APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed to be appropriate by the clinical expert consulted by the CADTH Common Drug Review. 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 INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 1 INFECTION**

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Total Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir/ velpatasvir (Epclusa) | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 60,000 |
| Sofosbuvir/ velpatasvir (Epclusa) plus RBV | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 63,045 to 63,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 mg to 1200 mg daily[b] | | 3,045 to 3,654 | |
| **Interferon-Free Regimens** | | | | | | | |
| Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) | 60 mg | tab | 428.5714[c] | 60 mg daily | 12 weeks[d] | 36,000 | 83,000 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 | |
| Daclatasvir (Daklinza) plus Asunaprevir (Sunvepra)<br><br>*Genotype 1b* | 60 mg | tab | 428.5714[c] | 60 mg daily | 24 weeks | 72,000 | NA |
| | 100 mg | tab | NA | 100 mg twice daily | | NA | |
| Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) plus RBV | 60 mg | tab | 428.5714[c] | 60 mg daily | 12 weeks[e] | 36,000 | 94,045 to 94,654 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 | |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1,000 mg to 1,200 mg daily | | 3,045 to 3,654 | |
| Elbasvir/ grazoprevir (Zepatier) | 50/100 mg | Tab | 717.8571[f] | 50/100 mg daily | 12 weeks[g] | 60,300 | 60,300 |

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Total Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Elbasvir/ grazoprevir (Zepatier) plus RBV | 50/100 mg | Tab | 717.8571[f] | 50/100 mg daily | 16 weeks[h] | 80,400 | 83,648 to 86,084 |
| | 200 mg<br>400 mg<br>600 mg | | 7.2500<br>14.5000<br>21.7500 | 800 to 1,400 mg daily | | 3,248 to 5,684 | |
| Ledipasvir / Sofosbuvir (Harvoni) | 90/400 mg | Tab | 797.6190 | 90/400 mg daily | 8 to 24 weeks[i] | 44,667<br>(8 weeks)<br>67,000 to 134,000<br>(12 to 24 weeks) | 44,667<br><br>67,000 to 134,000 |
| Ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (Holkira Pak) | 12.5/75/50 mg<br><br>250 mg | tabs | 665.0000[j] | 25/150/100 mg ombitasvir/ paritaprevir/ ritonavir daily + 250 mg dasabuvir twice daily | 12 weeks[k] | 55,860 | 55,860 |
| Ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (Holkira Pak) plus RBV | 12.5/75/50 mg<br>250 mg | tabs | 665.0000[j] | 25/150/100 mg ombitasvir/ paritaprevir/ ritonavir daily + 250 mg dasabuvir twice daily | 12 to 24 weeks[k] | 55,860 to 111,720 | 55,860 to 111,720 |
| | 200 mg<br>400 mg<br>600 mg | | 0.0001[j] | 1,000 to 1,200 mg daily | | | |
| Sofosbuvir (Sovaldi) plus RBV | 400 mg | tab | 654.7619 | 400 mg daily | 24 weeks[l] | 110,000 | 116,090 to 117,308 |
| | 200 mg<br>400 mg<br>600 mg | | 7.2500<br>14.5000<br>21.7500 | 1000 to 1200 mg daily | | 6,090 to 7,308 | |
| Simeprevir (Galexos) plus sofosbuvir (Sovaldi) | 150 mg | cap | 434.5500 | 150 mg daily | 12 to 24 weeks[m] | 36,502 to 73,004 | 91,502 to 183,004 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 to 110,000 | |
| **Direct-Acting Antivirals in Combination With Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Daclatasvir plus asunaprevir plus PR<br><br>*Genotype 1* | 60 mg | tab | 428.5714[c] | 60 mg daily | 24 weeks | 72,000 | NA |
| | 100 mg | tab | NA | 100 mg twice daily | | NA | |
| | 180 mcg/<br>200 mg | vial/tab | 407.3900 | 60 mg daily plus 100 mg twice daily + Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day | | 9,777 | |

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Total Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir (Sovaldi) plus PR | 400 mg | tab | 654.7619 | 400 mg daily | 12 weeks | 55,000 | 59,889 |
| | 180 mcg/ 200 mg | vial/tab | 407.3900 | Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg daily | | 4,889 | |
| Simeprevir (Galexos) plus 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 | Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day | 24 to 48 weeks[n] | 9,777 to 19,555 | |
| Boceprevir (Victrelis) plus PR | 200 mg | cap | 12.5000 | 800 mg three 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 | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day[m] | 28 to 48 weeks | 12,275 to 21,043 | |
| Boceprevir/ P2bR (Victrelis Triple) | 200/80/200<br>200/100/200<br>200/120/200<br>200/150/200<br><br>mg/mcg/mg | 168 caps+<br>2 pens+<br>56 caps | 2652.55[n]<br>2652.55[n]<br>2726.00[n]<br>2726.00[n] | Boceprevir 800 mg three times daily; Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400/day, initiate after 4 weeks Pegetron therapy | 24 to 44 weeks[p] | 31,831 to 59,972 | 31,831 to 59,972 |
| **Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Peginterferon alfa-2a + RBV (Pegasys RBV) | 180 mcg/ 200 mg | vial or syringe/<br>28 Tabs<br>35 Tabs<br>42 Tabs | 407.3900 | Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[j] | 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[o] | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day | 48 weeks | 19,043 | 19,043 |
| | 150 mcg/200 mg | 2 vials + 84 or 98 caps | 876.7800[o] | | | 21,043 | 21,043 |
| | 80 mcg/200 mg<br>100 mcg/200 mg<br>120 mcg/200 mg<br>150 mcg/200 mg | 2 pens / 56 to 98 caps | 802.9900<br>802.9900<br>887.3000<br>887.3000 | | | 19,272 to 21,295 | 19,272 to 21,295 |

HCV = hepatitis C virus; NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid.
Note: All prices are from the Saskatchewan Drug Plan online formulary (June 2016) unless otherwise indicated.
[a] Manufacturer's submitted price.
[b] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.
[c] Price from IMS Brogan DeltaPA (June 2016, Saskatchewan wholesale).
[d] For patients with HCV genotypes 1, 2, or 3, without cirrhosis or liver transplantation.
[e] For patients with HCV genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.
[f] Price from IMS Brogan Delta PA (April 2016, Association québécoise des pharmaciens propriétaires price). Zepatier is currently under review by the CADTH Common Drug Review for the treatment of HCV genotypes 1, 3, and 4.
[g] 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.
[h] For genotype 1a patients with treatment experience on-treatment virologic failure.
[i] 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 less than 6 million IU/mL.
[j] 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.
[k] 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 peg-IFN and RBV.
[l] For treatment-naive and treatment-experienced non-cirrhotic patients with genotype 1 who are ineligible to receive an interferon.
[m] 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.
[n] 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.
[o] Ontario Drug Benefit Exceptional Access Program (June 2016).
[p] Treatment duration is response-guided based on viral load.

**TABLE 5: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 2 INFECTION**

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir/ velpatasvir (Epclusa) | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 60,000 |
| Sofosbuvir/ velpatasvir (Epclusa) plus RBV | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 63,045 to 63,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 mg to 1200 mg daily[b] | | **3,045 to 3,654** | |
| **Interferon-Free Regimens** | | | | | | | |
| Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) | 60 mg | tab | 428.5714[c] | 60 mg daily | 12 weeks[d] | 36,000 to 72,000 | 83,000 to 138,000 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 to 110,000 | |
| Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) plus RBV | 60 mg | tab | 428.5714[c] | 60 mg daily | 12 weeks[e] | 36,000 | 94,045 to 94,654 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 | |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 mg to 1200 mg daily[b] | | 3,045 to 3,654 | |
| Sofosbuvir (Sovaldi) plus RBV | 400 mg | tab | 654.7619 | 400 mg daily | 12 weeks | 55,000 | 58,045 to 58,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 to 1200 mg daily | | 3,045 to 3,654 | |
| **Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Peginterferon alfa-2a + RBV (Pegasys RBV) | 180 mcg/200 mg | vial or syringe/ 28 tabs<br>35 tabs<br>42 tabs | 407.3900 | Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day | 48 weeks | 19,555 | 19,555 |

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Peginterferon alfa-2b + RBV (Pegetron) | 50 mcg /200 mg | 2 vials + 56 caps | 793.4700[f] | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day | 48 weeks | 19,043 | 19,043 |
| | 150 mcg/ 200 mg | 2 vials + 84 or 98 caps | 876.7800[f] | | | 21,115 | 21,115 |
| | 80 mcg/200 mg<br>100 mcg/200 mg<br>120 mcg/200 mg<br>150 mcg/200 mg | 2 pens / 56 to 98 caps | 802.9900<br>802.9900<br>887.3000<br>887.3000 | | | 19,043 to 21,115 | 19,043 to 21,115 |

HCV = hepatitis C virus; NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
Note: All prices are from the Saskatchewan Drug Plan online formulary (June 2016) unless otherwise indicated.
[a] Manufacturer's submitted price.
[b] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.
[c] Price from IMS Brogan Delta PA (June 2016, Saskatchewan wholesale).
[d] For patients with HCV genotypes 1, 2, or 3, without cirrhosis or liver transplantation.
[e] For patients with HCV genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.
[f] Ontario Drug Benefit Formulary Exceptional Access Program (June 2016).

**TABLE 6: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 3 INFECTION**

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir/ velpatasvir (Epclusa) | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 60,000 |
| Sofosbuvir/ velpatasvir (Epclusa) plus RBV | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 63,045 to 63,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 mg to 1200 mg daily[b] | | 3,045 to 3,654 | |
| **Interferon-Free Regimens** | | | | | | | |
| Daclatasvir (Daklinza) plus Sovaldi | 60 mg | tab | 428.5714[c] | 60 mg once daily | 12 weeks[d] | 36,000 to 72,000 | 91,000 to 182,000 |
| | 400 mg | cap | 654.7619 | 400 mg once daily | | 55,000 to 110,000 | |
| Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) plus RBV | 60 mg | tab | 428.5714[c] | 60 mg daily | 12 weeks[e] | 36,000 | 94,045 to 94,654 |
| | 400 mg | tab | 654.7619 | 400 mg daily | | 55,000 | |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1000 mg to 1200 mg daily[b] | | 3,045 to 3,654 | |
| Elbasvir/ grazoprevir (Zepatier) plus sofosbuvir (Sovaldi) | 100/50 mg | tab | 717.8571[f] | 50/100 mg once daily | 12 weeks | 60,300 | 115,300 |
| | 400 mg | cap | 654.7619 | 400 mg once daily | | 55,000 | |
| Sofosbuvir (Sovaldi) plus RBV | 400 mg | tab | 654.7619 | 400 mg once daily | 24 weeks | 110,000 | 116,090 to 117,308 |
| | 400 mg<br>600 mg | cap | 14.5000<br>21.7500 | 1000 to 1200 mg daily | | 6,090 to 7,308 | |
| **Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Peginterferon alfa-2a + RBV (Pegasys RBV) | 180 mcg/200 mg | vial or syringe/<br>28 tabs<br>35 tabs<br>42 tabs | 407.3900 | Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day | 48 weeks | 19,555 | 19,555 |

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Peginterferon alfa-2b + RBV (Pegetron) | 50 mcg/200 mg | 2 vials + 56 caps | 793.4700[g] | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day | 48 weeks | 19,043 | 19,043 |
| | 150 mcg/200 mg | 2 vials + 84 or 98 caps | 876.7800[g] | | | 21,043 | 21,043 |
| | 80 mcg/200 mg<br>100 mcg/200 mg<br>120 mcg/200 mg<br>150 mcg/200 mg | 2 pens / 56 to 98 caps | 802.9900<br>802.9900<br>887.3000<br>887.3000 | | | 19,272 to 21,295 | 19,272 to 21,295 |

HCV = hepatitis C virus; NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
Note: All prices are from the Saskatchewan Drug Plan online formulary (June 2016) unless otherwise indicated.
[a] Manufacturer's price.
[b] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.
[c] Price from IMS Brogan Delta PA (June 2016, Saskatchewan wholesale).
[d] For patients with HCV genotypes 1, 2, or 3, without cirrhosis or liver transplantation.
[e] For patients with HCV genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.
[f] Price from IMS Brogan DeltaPA (April 2016, Association québécoise des pharmaciens propriétaires price). Zepatier is currently under review by the CADTH Common Drug Review for the treatment of HCV genotypes 1, 3, and 4.
[g] Ontario Drug Benefit Exceptional Access Program (June 2016).

**TABLE 7: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 4 INFECTION**

| Drug / Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Total Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir/ velpatasvir (Epclusa) | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 60,000 |
| Sofosbuvir/ velpatasvir (Epclusa) plus RBV | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 63,045 to 63,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1,000 mg to 1200 mg daily[b] | | 3,045 to 3,654 | |
| **Interferon-free Regimens** | | | | | | | |
| Elbasvir/ grazoprevir (Zepatier) | 50/100 mg | tab | 717.8571[b] | 50/100 mg once daily | 12 weeks[c] | 60,300 | 60,300 |
| Elbasvir/ grazoprevir (Zepatier) plus RBV | 100/50 mg | tab | 717.8571[b] | 50/100 mg once daily | 16 weeks[d] | 80,400 | 61,915 to 64,351 |
| | 200 mg<br>400 mg<br>600 mg | | 7.2500<br>14.5000<br>21.7500 | 800 mg to 1400 mg daily | | 3,248 to 5,684 | |
| Ombitasvir/ paritaprevir/ ritonavir (Technivie) plus RBV | 12.5 mg<br>75 mg<br>50 mg | tab | 665.0000 per two tabs | 25/150/100 mg once daily | 12 weeks[c] | 55,860 | 58,905 to 59,514 |
| | 200 mg<br>400 mg<br>600 mg | | 7.2500<br>14.5000<br>21.7500 | 1,000 to 1,200 mg daily | | 3,045 to 3,654 | |
| Simeprevir (Galexos) plus sofosbuvir (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 | |

| Drug / Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Total Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| **Direct-Acting Antivirals in Combination With Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Daclatasvir (Daklinza) plus Asunaprevir (Sunvepra) plus PR | 60 mg | tab | 428.5714[f] | 60 mg once daily | 24 weeks | 72,000 | NA |
| | 100 mg | tab | NA | 100 mg twice daily | | NA | |
| | 180 mcg/200 mg | vial/tab | 407.3900 | Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day | | 9,777 | |
| Sovaldi (sofosbuvir) plus PR | 400 mg | tab | 654.7619 | 400 mg once daily | 12 weeks | 55,000 | 59,889 |
| | 180 mcg/ 200 mg | vial/tab | 407.3900 | Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day | | 4,889 | |
| Simeprevir (Galexos) plus PR | 150 mg | Cap | 434.5500 | 150 mg once daily | 12 weeks[g] | 36,502 | 46,279 to 56,057 |
| | 180 mcg/200 mg | vial/tab | 407.3900 | Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day | 24 to 48 weeks[h] | 9,777 to 19,555 | |
| **Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Peginterferon alfa-2a + RBV (Pegasys RBV) | 180 mcg/200 mg | vial or syringe/ 28 tabs 35 tabs 42 tabs | 407.3900 | Peg-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[h] | 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[i] | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day | 48 weeks | 19,043 | 19,043 |
| | 150 mcg/200 mg | 2 vials + 84 or 98 caps | 876.7800[i] | | | 21,043 | 21,043 |
| | 80 mcg/200 mg<br>100 mcg/200 mg<br>120 mcg/200 mg<br>150 mcg/200 mg | 2 pens / 56 to 98 caps | 802.9900<br>802.9900<br>887.3000<br>887.3000 | | | 19,272 to 21,295 | 19,272 to 21,295 |

NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (Apr 2016) unless otherwise indicated.
[a] Manufacturer's price.
[b] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.
[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] Price from IMS Brogan Delta PA (June 2016, Saskatchewan wholesale).
[g] 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.
[h] Forty-eight weeks for genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV coinfection.
[i] Ontario Drug Benefit Formulary, Exceptional Access Program (June 2016).

**TABLE 8: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPES 5 AND 6 INFECTION**

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Sofosbuvir/ velpatasvir (Epclusa) | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 60,000 |
| Sofosbuvir/ velpatasvir (Epclusa) plus RBV | 400/100 mg | tab | 714.2857[a] | 400/100 mg daily[b] | 12 weeks | 60,000 | 63,045 to 63,654 |
| | 200 mg<br>400 mg<br>600 mg | tab | 7.2500<br>14.5000<br>21.7500 | 1,000 mg to 1,200 mg daily[b] | | 3,045 to 3,654 | |
| | 400 mg<br>600 mg | cap | 14.5000<br>21.7500 | 1,000 to 1,200 mg daily | | 6,090 to 7,308 | |
| **Interferon-Free Regimens** | | | | | | | |
| Ledipasvir / Sofosbuvir (Harvoni)[c,d] | 90/400 mg | tab | 797.6190 | 90/400 mg daily | 12 weeks | 44,667<br>(8 weeks)<br>67,000 to 134,000<br>(12 to 24 weeks) | 44,667<br><br>67,000 to 134,000 |
| **Direct-Acting Antivirals in Combination With Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Sovaldi (sofosbuvir) plus PR[d] | 400 mg | tab | 654.7619 | 400 mg once daily | 12 weeks | 55,000 | 59,889 |
| | 180 mcg/200mg | vial/tab | 407.3900 | Peg-IFN<br>180 mcg/week; RBV 800 to 1,200 mg/day | | 4,889 | |
| **Peginterferon Alfa Plus RBV Therapy** | | | | | | | |
| Peginterferon alfa-2a + RBV (Pegasys RBV) | 180 mcg/200 mg | vial or syringe/<br>28 tabs<br>35 tabs<br>42 tabs | 407.3900 | Peg-IFN<br>180 mcg/week; RBV<br>1,000 to 1,200 mg/day | 48 weeks | 19,555 | 19,555 |

| Drug/ Comparator | Strength | Dosage Form | Price, $ | Recommended Dose | Duration | Cost for 1 Course of Therapy, $ | Cost for 1 Course of Combo Therapy, $ |
|---|---|---|---|---|---|---|---|
| Peginterferon alfa-2b + RBV (Pegetron) | 50 mcg/200 mg | 2 vials + 56 caps | 793.4700[e] | Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day | 48 weeks | 19,043 | 19,043 |
| | 150 mcg/200 mg | 2 vials + 84 or 98 caps | 876.7800[e] | | | 21,043 | 21,043 |
| | 80mcg/200mg<br>100mcg/200mg<br>120mcg/200mg<br>150mcg/200mg | 2 pens / 56 to 98 caps | 802.9900<br>802.9900<br>887.3000<br>887.3000 | | | 19,272 to 21,295 | 19,272 to 21,295 |

HCV = hepatitis C virus; NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
Note: All prices are from the Saskatchewan Drug Plan online formulary (June 2016) unless otherwise indicated.
[a] Manufacturer's price.
[b] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.
[c] Not indicated, but recommended for genotype 5 in the 2015 Consensus Guidelines from the Canadian Association for the Study of the Liver.[6]
[d] Not indicated, but recommended for genotype 6 in the 2015 Consensus Guidelines from the Canadian Association for the Study of the Liver.[6]
[e] Ontario Drug Formulary Benefit Exceptional Access Program (June 2016).

# APPENDIX 2: ADDITIONAL INFORMATION

**TABLE 9: SUBMISSION QUALITY**

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | | | X |
| *Comments*<br>*Reviewer to provide comments if checking "no"* | The description of monitoring costs, in particular, is very poor. | | |
| Was the material included (content) sufficient? | | | X |
| *Comments*<br>*Reviewer to provide comments if checking "poor"* | The manufacturer's model and the material that can be generated from this, particularly in genotypes 4/5/6, is poor. | | |
| Was the submission well organized and was information easy to locate? | | | X |
| *Comments*<br>*Reviewer to provide comments if checking "poor"* | The manufacturer's model and the description of the model from the Pharmacoeconomic Report differ. | | |

**TABLE 10: AUTHOR INFORMATION**

| Authors | Affiliations |
|---|---|
| Athena Research Inc.<br>MAPI Group UK | |

| | 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 | | | Rights not requested |

# APPENDIX 3: REVIEWER WORKSHEETS

## 1. Manufacturer's model structure

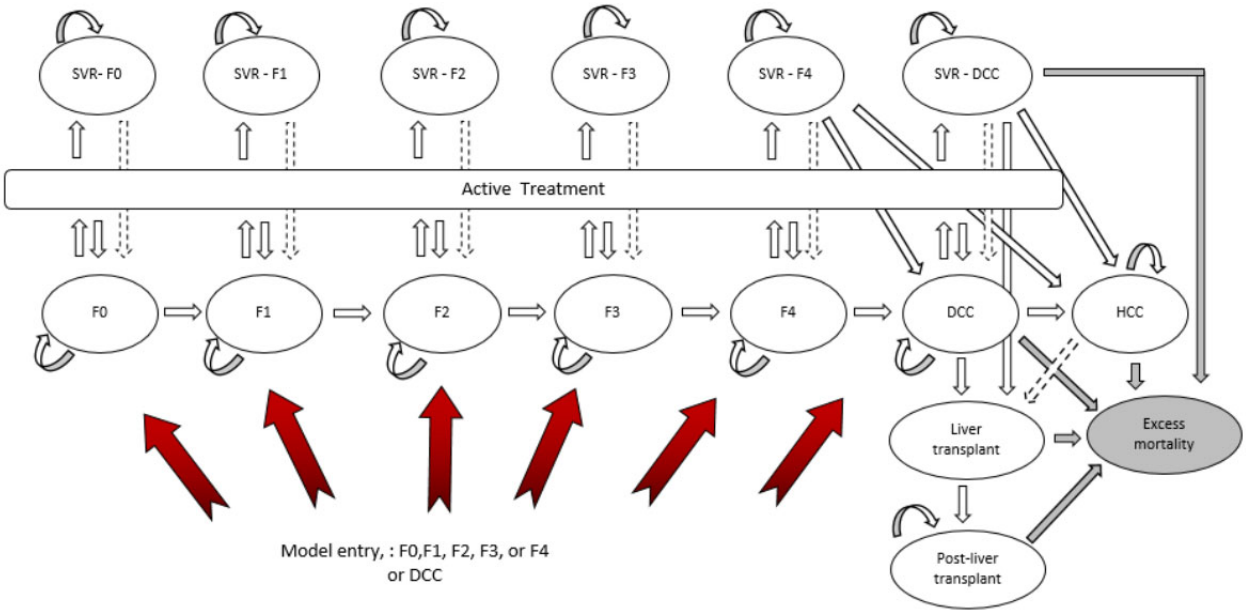
The manufacturer's model structure was adapted from a model designed for interferon in 1997 by Bennett, and subsequently adapted.[7-9] The manufacturer claimed that this was used in support of both applications for sofosbuvir (SOF) and for ledipasvir (LDV)/SOF. The model structure includes separate states for each Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis score (F0 to F4) plus decompensated cirrhosis (DCC). In addition, each of these five states also has a corresponding sustained virologic response (SVR) analogue in the manufacturer model (e.g., as SVR-F0 to SVR-F4 and SVR-DCC). In separating out the METAVIR states, the manufacturer has responded to the CADTH Common Drug Review's (CDR's) critique of a prior submission.

States subsequent to METAVIR states and DCC include a single hepatocellular carcinoma (HCC) state , as well as a first-year liver transplant state (LT1) and a post-liver transplant state (LT2). (Abbreviations have been added for the last two states for the purposes of clarity & brevity.)

Within the model, there is an allowance for transition between each (non-SVR) METAVIR state to the next state, plus transitions from both F4 and SVR-F4 to DCC and HCC. From DCC, transitions may occur to HCC and LT1, with transitions from HCC to LT1 only considered in sensitivity analyses. Excess mortality from the disease is assessed from all states subsequent to those based on METAVIR.

The model also considers the potential for reinfection from SVR states back to the corresponding non-SVR METAVIR states within sensitivity analysis. As with separating out the METAVIR states, this appears to reflect feedback from CDR's critique of a prior submission.

**FIGURE 2: MANUFACTURER'S MODEL STRUCTURE**




DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[10]

The model used two-week transition probabilities for the first 36 cycles (hence, 72 weeks), followed by one cycle of 24 weeks (hence, to 96 weeks), and then yearly thereafter.

The manufacturer presents results for 26 separate subgroups. Twenty-four of these subgroups were formed by considering all combinations of genotype (as 1a, 1b, 2, 3, 4, and combined 5/6), prior treatment exposure (treatment-naive [TN] or treatment-experienced [TE]), and cirrhosis status (non-cirrhotic [NC] as F0 to F3, or compensated cirrhosis [CC] as F4). The final two subgroups consider all patients with DCC, separating those who were treatment-naive and those who were treatment-experienced.

The manufacturer compares SOF/velpatasvir (VEL) against a number of comparators, being all licensed and funded comparators, as well as SOF/daclatasvir (DCV) for genotype 3 NC, and EBR/GZR = elbasvir/grazoprevir (EBR/GZR). The manufacturer excludes a number of older treatments due to perceived obsolescence. The model results include a number of comparators but typically exclude both No Treatment and interferon-based regimens, except for genotypes 2 (TN) and 3 (TN), where pegylated interferon plus ribavirin (PR) is included but No Treatment is excluded, and genotypes 5/6, where both PR and No Treatment results are included.

The natural history transition rates (including chronic hepatitis C [CHC] infection–related mortality) are based upon a number of different studies, but the annual probabilities correspond with those used in the CADTH Therapeutic Review. As the manufacturer's model includes potential treatment for those in DCC, the model allows for a DCC-SVR transition, with the transition probabilities based on data from van der Meer et al.[11]

The effectiveness data for SOF/VEL are taken as SVR-12 rates within the active arms of the four phase 3 trials: ASTRAL-1,[11] ASTRAL-2 and ASTRAL-3,[3] and ASTRAL-4.[4] For patients with no cirrhosis or with CC, these trials compared 12 weeks SOF/VEL to either placebo (ASTRAL-1) or 12 or 24 weeks of SOF + RBV (ASTRAL-2, ASTRAL-3). ASTRAL-4 compared SOF/VEL + RBV against 12- and 24-week SOF/VEL regimens in patients with DCC.

ASTRAL-1 considered genotypes 1, 2, 4, 5, and 6. It is worth noting that the comparator group in ASTRAL-1 is not included as a comparator in the manufacturer's model for genotypes 1a, 1b, 2, or 4, although it is included (in effect) as no treatment for genotypes 5 and 6. Note that while ASTRAL-4 included a number of SOF/VEL-based regimens, not all these comparators are included in the modelling for DCC. ASTRAL-2 and ASTRAL-3 considered a total of 1,199 patients in genotypes 2 and 3, and the comparator used in these trials also appears among the comparators in the modelling.

Due to the selection of comparators, direct comparisons reflecting observed data do not appear in the model in a majority of cases. There was no formal "indirect comparison" of results, as the manufacturer considered its results to be robust. Instead, naive direct comparisons were conducted from pivotal clinical trials. In many cases, the manufacturer claims a 100% SVR rate from its own trials for SOF/VEL, without making it clear within the Pharmacoeconomic Report the number of patients from whom these figures were obtained. With 20 distinct scenarios (covering genotypes 1a, 1b, 2, 4, 5/6), average sample size in each of these scenarios is likely to be low and a sample SVR value of 100% is unlikely to reflect the true (population) parameter. (Further detail on actual sample sizes is available in the main text.)

Utility data were taken from multiple sources, including increments for SVR (0.07) and decrements for interferon- and RBV-containing regimens (0.02) from the recent CADTH Therapeutic Review.[1] Utility data

were taken from a variety of studies, but were broadly consistent with the CADTH Therapeutic Review.[1] In contrast to the review, however, the manufacturer did not assign a disutility to adverse events, including anemia. Costs were broken down into drug costs, monitoring costs, adverse event costs, and health state–related costs.

Drug treatment costs were obtained from provincial formularies, and corresponded to the CADTH Therapeutic Review.[1] Adverse event costs were taken from the CADTH review, although the manufacturer noted that these costs differ from the costs used previously, where anemia costs were higher ($2,6696.85) than in the CADTH Therapeutic Review ($515.10). Monitoring costs were obtained using a large number of discrete cost items, but there is no clear breakdown in the manufacturer's submitted report for how these costs are computed. Table 12 of the manufacturer's report,[10] which details the modelled figures as provided in the model, appears below.

**FIGURE 3: MANUFACTURER'S MONITORING COSTS (MS TABLE 12)**

| Patient Population | Cirrhosis Status | Duration of Therapy | Total Costs |
|---|---|---|---|
| All patients | no | Cycle 1 only: initial diagnostic work-up | $586 |
| | yes | | $1,375 |
| Patients receiving any active treatment | both no and yes | Cycle 1 only: at treatment start | $720 |
| Patients receiving no treatment | no | one year of no treatment | $205 |
| | yes | | $409 |
| All non-IFN treatments | both no and yes | 4 weeks of treatment | $900 |
| | | 6 weeks of treatment | $900 |
| | | 8 weeks of treatment | $1,239 |
| | | 12 weeks of treatment | $1,459 |
| | | 16 weeks of treatment | $1,678 |
| | | 24 weeks of treatment | $1,898 |
| | no | 24 weeks of treatment | $2,873 |
| | yes | | $4,223 |
| | no | 36 weeks of treatment | $3,365 |
| | yes | | $4,935 |
| | no | 48 weeks of treatment | $4,092 |
| | yes | | $7,582 |

IFN = interferon.
Source: Manufacturer's pharmacoeconomic submission.[10]

Given the size of many of these figures, a clear explanation of what these figures entail and how they are justified was anticipated. Instead, the reader is instructed that this is "outlined in the model", and this is not straightforward. With a monitoring cost exceeding $7,500 over the course of some treatments, it is clear that some clarity is required. For these final costs, there are a total of 24 separate outpatient visits to a consultant, rather than other types of less intensive visits — despite some of these being labelled as "basic checks". The final figure also appears to include costs for interferon (IFN)-based treatment up to week 22, despite being labelled as a "non-IFN treatment". These monitoring costs do not appear to be appropriate.

The manufacturer does not sufficiently explain or motivate its approach and some of the figures provided appear to lack face validity. As an example, a mixed cohort of CC and NC patients receiving 24 weeks of non-IFN treatment have an average cost of $1,898. Taken separately, however, monitoring costs for CC patients are $2,873 and NC patients are $4,223, so it is difficult to see how the average of these two figures could be nearly $1,000 lower than either of the two figures that would need to be averaged. The manufacturer also includes a monitoring cost of "No Treatment", despite also including a

cost attached to each health state. It is unclear why the manufacturer has assumed a specific monitoring cost of undertaking no activity.

The CADTH Therapeutic Review did not include costs of monitoring beyond those already counted within the general health state costs.[1] The health state–related costs within the METAVIR states were based on clinical opinion, which suggests yearly monitoring costs of $390 with active infection and $0 with SVR. The remaining costs are said to come from the CADTH Therapeutic Review (or are consistent with it). However, the treatment of costs in HCC is not consistent with the Therapeutic Review. The review states that the "late phase" is intended to begin with a diagnosis of DCC or HCC, or both, and attract a cost figure of $14,597 per annum. In the model, this $14,597 is used for the DCC state but $45,207 is instead used for the HCC state. As with the monitoring costs, this appears inappropriate.

**2. Data sources**

| Data Input | Description of Data Source | CDR Comment |
|---|---|---|
| Efficacy | The effectiveness estimate (SVR rates) were taken from the active intervention arms of pivotal trials. | There is a high potential for bias in the estimates produced by observed SVR rates in the clinical trials. Uncertainty in SVR estimates not appropriately captured in the model. |
| Natural history | The natural history transition rates (including CHC-related mortality) are drawn from a number of different studies. | The annual probabilities correspond with those used in the CADTH Therapeutic Review.[1] |
| Utilities | Utilities are taken from a variety of sources, including the CADTH Therapeutic Review.[1] | Where applied, the utilities used appear to correspond to the CADTH Therapeutic Review in all cases. However, the utilities for adverse events were not considered. |
| Resource use | The manufacturer considers costs for health states, drug acquisition, and adverse events.<br><br>In most cases, the manufacturer does not explicitly consider resource utilization as distinct from costs. The manufacturer uses clinical judgment to formulate scenarios for monitoring costs, using provincial formulary unit costs to obtain cost figures. | The manufacturer's approach to estimating monitoring costs is not discussed in full within the Pharmacoeconomic Report. |
| AEs (Indicate which specific AEs were considered in the model) | The model considers 3 AEs: Anemia, Depression, and Rash.<br><br>A single discontinuation rate was assumed for each regimen by prior treatment exposure across all scenarios, including the impact of discontinuation. SOF/VEL + RBV had the highest AE-based discontinuation rates (4.6% over 12 weeks) based on AEs for any regimen other than PR (10.7% for 24 weeks, 14% for 48 weeks). | This approach is consistent with several prior CADTH reviews.<br><br>There was little justification for the use of a single discontinuation rate. |
| Mortality | Age and gender specific mortality rates were taken from Health Canada. Annual background mortality was applied to patients in all health states.[12] | The CADTH Therapeutic Review made similar assumptions. |

| Data Input | Description of Data Source | CDR Comment |
|---|---|---|
| | Excess mortality data were applied to the decompensated cirrhotic, transplant, and hepatocellular cancer states.[13-15] | |
| Costs | | |
| Drug | From provincial formularies, as per the CADTH Therapeutic Review.[1] | For RBV, the dose is weight dependent and an assumed weight of 80 kg is used. This is taken from a systematic review and may not represent the actual weight of patients observed in clinical practice. This may affect the external validity of the drug costs used in the analysis. |
| AEs | RAMQ Database study by Lachaine et al.[16] | Majority (95.2%) of patients included in the Lachaine study were treated with PR only, which means that duration of PR exposure (and associated anemia and costs) was longer (48 weeks) than what is likely to be observed in current practice. |
| Health state | Based on CADTH Therapeutic Review.[1]<br><br>Based on expert opinion for F0-F3 and SVR F0-F3. | While the authors state an extra source for costs following liver transplantation, the same source was used by the CADTH Therapeutic Review.<br>No costs were assumed following SVR within these states, including any monitoring or support for existing fibrosis. |
| Monitoring | The manufacturer states that data were obtained by clinical opinion. | See above. |

AE = adverse event; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; PR = pegylated interferon plus ribavirin; RAMQ = Régie de l'assurance maladie du Québec; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; VEL = velpatasvir.

### 3. Manufacturer's key assumptions

| Assumption | CDR Comment |
|---|---|
| The manufacturer uses ASTRAL-1 to provide multiple scenarios covering a large population of cirrhotic and/or treatment-experienced patients. | The ASTRAL-1 data are separated across 20 distinct subgroups, so the overall SVR12 rate is not necessarily relevant. |
| Naive direct comparisons are provided for effectiveness data. | Neither ASTRAL-1 nor ASTRAL-4 include any trial comparators within the comparators in the model; hence, information from non-relevant comparators in these trials is discarded. An "indirect treatment comparison" may have utilized this information. |
| The manufacturer assumes large monitoring costs based only on clinical opinion. | The manufacturer also considers per-patient monitoring costs (up to $7,582). These costs assume a very large number of consultant visits. |
| No utilities are assessed for adverse events. | SOF/VEL + RBV has a high rate of discontinuation due to adverse events. Assuming that adverse events do not affect patient utilities may bias results. |
| HCC health state is assigned a distinct, much higher cost than DCC. | HCC health state costs are classified as "late stage" costs within the categories of the CADTH Therapeutic Review (i.e., the same cost is applied to DCC and HCC states).[1] Using the approach of the CADTH review, the costs per year are around one-third of the cost applied by the manufacturer. |

CDR = CADTH Common Drug Review; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; VEL = velpatasvir.

### 4. Manufacturer's results

The manufacturer's results from the deterministic analysis are summarized in the main text. Full versions of the manufacturer's results appear in Tables 1-1 to 1-26 of the manufacturer's report.[10] In most cases, these deterministic results are likely to be biased and caution must be used in interpreting these as an accurate record of likely outcomes. In many cases, the results provided by the manufacturer also claim that SOF/VEL dominates other alternatives or is dominated by other alternatives, and so setting out ICURs is of limited relevance.

As such, the broad summaries presented in Figures 1 and 2 provide the best indication of likely results without providing false reassurance or unnecessary detail.
There are, however, several cases in which there is some value in setting out results:

- Genotype 1b, treatment-naive, non-cirrhotic subgroup (as SOF/VEL does not appear to be cost-effective but is not dominated)
- Genotype 1b, treatment-naive, cirrhotic subgroup (as SOF/VEL does not appear to be cost-effective but is not dominated)
- Genotype 3, treatment-naive, non-cirrhotic subgroup (as there is uncertainty about which option is cost-effective)
- Genotype 3, treatment-naive, cirrhotic subgroup (as SOF/VEL appears to be possibly cost-effective but does not dominate)
- Genotype 4, treatment-experienced non-cirrhotic subgroup (as SOF/VEL is not cost-effective and it is unclear which option is cost-effective).

**TABLE 11: SUMMARY OF MANUFACTURER'S BASE-CASE RESULTS — GENOTYPE 1B, TREATMENT-NAIVE, NON-CIRRHOTIC SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) |
|---|---|---|---|
| EBR/GZR x 8 | $44,990 | 11.97 | Baseline |
| EBR/GZR x 12 | $64,468 | 11.98 | Dominated |
| LDV/SOF x 8 | $48,093 | 12.06 | ~$37,000 (vs. GZR/EBR) |
| LDV/SOF x 8/12 | $63,334 | 12.07 | Dominated |
| LDV/SOF x 12 | $69,997 | 12.08 | Dominated |
| OMB/PAR/r + RBV x 12 | $58,199 | 12.08 | Extendedly dominated |
| SOF/VEL x 12 | $62,666 | 12.10 | $332,533 (vs. LDV/SOF x 8) |

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

In this case, there is a relatively low difference in QALYs reported between LDV/SOF (x 8) and SOF/VEL, but around a $14,000 difference in costs. The SOF/VEL treatment does not appear to be cost-effective, despite dominating several other options in head-to-head comparisons.

**TABLE 12: REANALYSIS OF MANUFACTURER'S BASE-CASE RESULTS — GENOTYPE 1B, TREATMENT-NAIVE, CIRRHOTIC SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) |
|---|---|---|---|
| EBR/GZR x 12 | $105,961 | 10.78 | Dominated |
| OMB/PAR/r + RBV x 12 | $104,192 | 10.87 | Baseline |
| SOF/VEL x 12 | $104,998 | 10.88 | $233,740 |
| LDV/SOF x 12 | $111,993 | 10.88 | Dominated |

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.

Again, there is a very low QALY benefit for SOF/VEL over a comparator treatment at a lower price.

**TABLE 13: REANALYSIS OF MANUFACTURER'S BASE-CASE RESULTS — GENOTYPE 3, TREATMENT-NAIVE, NON-CIRRHOTIC SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) |
|---|---|---|---|
| PR x 24 | $24,984 | 11.41 | Baseline |
| SOF + RBV x 24 | $123,629 | 11.86 | Dominated |
| SOF + DCV x 12 | $94,514 | 12.04 | Dominated |
| SOF/VEL x 12 | $63,431 | 12.06 | ~$60,000 |
| EBR/GZR + SOF x 12 | $118,162 | 12.1 | ~$1,400,000 |

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

In this case, SOF/VEL does not appear to be cost-effective but has an ICUR close to an indicative $50,000 per QALY. The more effective alternative (EBR/GZR) has a far higher price and seems unlikely to be cost-effective. In this case, there are significant uncertainties as to cost-effectiveness but no clear reason to suspect SOF/VEL is cost-effective.

**TABLE 14: REANALYSIS OF MANUFACTURER'S BASE-CASE RESULTS — GENOTYPE 3, TREATMENT-NAIVE, CIRRHOTIC SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) |
|---|---|---|---|
| PR x 24 | $84,471 | 8.44 | Baseline |
| SOF + RBV x 24 | $172,146 | 9.95 | Dominated |
| EBR/GZR + SOF x 12 | $164,196 | 10.56 | Dominated |
| SOF/VEL x 12 | $107,839 | 10.63 | $10,662 |

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.

There appears to be a clear case (at least on the basis of deterministic results) for SOF/VEL to be considered cost-effective here.

**TABLE 15: REANALYSIS OF MANUFACTURER'S BASE-CASE RESULTS — GENOTYPE 4, TREATMENT-EXPERIENCED, NON-CIRRHOTIC SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) |
|---|---|---|---|
| EBR/GZR x 12 | $69,869 | 11.62 | Dominated |
| EBR/GZR + RBV x 16 | $85,730 | 12.09 | Dominated |
| SOF + PR x 12 | $61,375 | 12.10 | Unclear |
| OMB/PAR/r + RBV x 12 | $61,790 | 12.10 | Unclear |
| SOF/VEL x 12 | $62,242 | 12.10 | Unlikely to be cost-effective |

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.

In this case, there are several options that have the same stated QALY benefits (to two significant figures), of which SOF + PR is the least expensive. Given the small difference in costs, OMB/PAR/r + RBV might be cost-effective with even a small difference in QALYs (measured with more precision), but the larger difference in costs for SOF/VEL makes cost-effectiveness unlikely.

**5. CADTH Common Drug Review Reanalysis**

**Genotypes 1a and 1b**

In the manufacturer's model, SOF/VEL is suggested to dominate in three of four genotype 1a subgroups, with LDV/SOF cost-effective in the remaining case (treatment-naive, non-cirrhotic). In the revised model (Table 16), this is no longer the case, primarily because a No Treatment option is now considered. In the three previously dominated cases, SOF/VEL appears to be cost-effective with ICURs below $15,000 per QALY versus No Treatment in each case. Note that even in these cases, there remains significant uncertainty about cost-effectiveness, with a 42% to 61% chance that a different treatment is cost-effective. In the final genotype 1a subgroup, LDV/SOF appears to be cost-effective in around 50% of cases, with SOF/VEL having only a 13% chance of being cost-effective at $50,000 per QALY.

**TABLE 16: REANALYZED MODELS, GENOTYPE 1A SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) | PROB(CE) |
|---|---|---|---|---|
| **Treatment-naive, non-cirrhotic** | | | | |
| NT | $33,527 | 10.075 | Baseline | 0% |
| LDV/SOF x 8 | $49,264 | 11.960 | $8,347 vs. NT | 50% |
| EBR/GZR x 12 | $63,973 | 11.978 | DOM | 7% |
| LDV/SOF x 8/12 | $64,136 | 12.023 | DOM | 10% |
| SOF/VEL x 12 | $63,348 | 12.030 | DOM | 13% |
| OMB/PAR/r + DSV + RBV x 12 | $62,345 | 12.032 | $183,586 vs. LDV/SOF | 15% |
| LDV/SOF x 12 | $70,045 | 12.047 | $507,678 vs. OMB/PAR/r+ DAS + RBV | 5% |
| **Treatment-naive, cirrhotic** | | | | |
| NT | $83,423 | 7.337 | Baseline | 0% |
| LDV/SOF x 12 | $115,389 | 10.546 | DOM | 9% |
| OMB/PAR/r + DAS + RBV x 12 | $106,888 | 10.602 | DOM | 17% |
| EBR/GZR x 12 | $105,561 | 10.781 | DOM | 34% |
| SOF/VEL x 12 | $105,364 | 10.820 | $6,300 vs. NT | 39% |
| **Treatment-experienced, non-cirrhotic** | | | | |
| NT | $36,508 | 9.944 | Baseline | 0% |
| EBR/GZR x12 | $63,497 | 11.976 | DOM | 20% |
| EBR/GZR + RBV x16 | $85,999 | 11.995 | DOM | 1% |
| OMB/PAR/r + DAS + RBV x 12 | $62,214 | 12.008 | EXT DOM | 30% |
| LDV/SOF x 12 | $70,151 | 12.009 | DOM | 11% |
| SOF/VEL x 12 | $62,307 | 12.060 | $12,195 vs. NT | 39% |
| **Treatment-experienced, cirrhotic** | | | | |
| NT | $83,451 | 7.333 | Baseline | 0% |
| OMB/PAR/r + DAS + RBV x 12 | $108,227 | 10.369 | DOM | 9% |
| EBR/GZR x16 | $107,439 | 10.502 | DOM | 19% |
| OMB/PAR/r + DAS + RBV x 24 | $160,863 | 10.714 | DOM | 0% |
| EBR/GZR + RBV x 16 | $126,586 | 10.811 | DOM | 13% |
| LDV/SOF x 24 | $176,502 | 10.815 | DOM | 0% |
| SOF/VEL x12 | $103,954 | 10.818 | $5,883 vs NT | 58% |

CE = cost-effectiveness; DAS = dasabuvir; DOM = dominated; EBR = elbasvir; EXT = extended; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; NT = No Treatment; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

For genotype 1b, the manufacturer's main results suggest that SOF/VEL is cost-effective only in the case of treatment-experienced, non-cirrhotic patients. In the remaining cases, LDV/SOF appears to be cost-effective in treatment-naive, non-cirrhotic patients, and OMB/PAR/r + DAS + RBV is most cost-effective in the remaining two cases where patients present with compensated cirrhosis.

The revised results in this case are provided in Table 17. Here, again, the only case where SOF/VEL appears to be cost-effective is the treatment-experienced non-cirrhotic case. Note that even here, SOF/VEL has only a 40% likelihood of being cost-effective compared with a 32% likelihood that

OMB/PAR/r + DAS + RBV is cost-effective. For treatment-naive, non-cirrhotic patients, SOF/VEL has only a 5% likelihood of being cost-effective at $50,000 per QALY. In the remaining cirrhotic cases, OMB/PAR/r + DAS + RBV x 12 appears to be cost-effective, with SOF/VEL having a 28% and 31% likelihood of cost-effectiveness at this indicative threshold value.

Overall, the results of the revised model do not appear to differ greatly from the manufacturer's reported analyses in the genotype 1a and 1b cases.

**TABLE 17: REANALYZED MODELS, GENOTYPE 1B SUBGROUPS**

| | Costs | QALYs | ICUR (per QALY) | Prob(CE) |
|---|---|---|---|---|
| **Treatment-naive, non-cirrhotic** | | | | |
| NT | $33,489 | 10.069 | Baseline | 2% |
| EBR/GZR x 12 | $63,972 | 11.975 | DOM | 1% |
| EBR/GZR x 8 | $44,588 | 11.978 | $5,815 vs. NT | 36% |
| LDV/SOF x 8 | $47,701 | 12.055 | $40,197 vs. EBR/GZR | 40% |
| SOF/VEL x 12 | $62,825 | 12.059 | DOM | 5% |
| LDV/SOF x 8/12 | $63,337 | 12.070 | DOM | 5% |
| LDV/SOF x 12 | $69,486 | 12.079 | DOM | 1% |
| OMB/PAR/r + RBV x 12 | $57,699 | 12.085 | $338,926 vs. LDV/SOF | 12% |
| **Treatment-naive, cirrhotic** | | | | |
| NT | $83,544 | 7.332 | Baseline | 0% |
| EBR/GZR x12 | $105,444 | 10.789 | DOM | 25% |
| OMB/PAR/r + DAS + RBV x 12 | $104,541 | 10.805 | $6,047 vs. NT | 29% |
| LDV/SOF x 12 | $112,349 | 10.810 | DOM | 18% |
| SOF/VEL x 12 | $105,337 | 10.810 | $143,155 vs. OMB/PAR/r + DAS + RBV | 28% |
| **Treatment-experienced, non-cirrhotic** | | | | |
| NT | $36,590 | 9.941 | Baseline | 0% |
| EBR/GZR x 12 | $63,500 | 11.975 | DOM | 20% |
| LDV/SOF x 12 | $70,453 | 11.987 | DOM | 8% |
| OMB/PAR/r + DAS + RBV x 12 | $61,966 | 12.027 | EXT DOM | 32% |
| SOF/VEL x 12 | $62,304 | 12.062 | $12,126 vs. NT | 40% |
| **Treatment-experienced, cirrhotic** | | | | |
| NT | $83,331 | 7.331 | Baseline | 0% |
| EBR/GZR x1 2 | $107,359 | 10.497 | DOM | 17% |
| SOF/VEL x 12 | $106,072 | 10.637 | DOM | 31% |
| OMB/PAR/r + DAS + RBV x 12 | $103,206 | 10.796 | $5,736 vs. NT | 52% |
| LDV/SOF x24 | $176,503 | 10.821 | $2,890,126 vs. OMB/PAR/r + DAS + RBV | 0% |

CE = cost-effectiveness; DAS = dasabuvir; DOM = dominated; EBR = elbasvir; EXT = extended; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; NT = No Treatment; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

**Genotype 2 subgroups**

Within the original manufacturer report, SOF/VEL was found to be cost-effective across all four subgroups and to dominate all alternatives in two of four cases. The rerun models appear to produce quite different findings, however, with PR providing a cheaper treatment option than no treatment in the two (treatment-naive) cases in which it is considered. In the treatment-naive, non-cirrhotic case, PR has a 93% likelihood of being cost-effective, with SOF/VEL having an ICUR of around $120,000 per QALY against this option. In the treatment-naive, cirrhotic case, the ICUR for SOF/VEL against PR is $27,364 per QALY, and SOF/VEL has a 66% likelihood of cost-effectiveness.

In the remaining two cases, SOF/VEL appears to be cost-effective at relatively low ICUR values against No Treatment ($12,196 per QALY and $6,000 per QALY) and presents with a high likelihood of being cost-effective (73%, 97%).

**TABLE 18: REANALYZED MODEL, GENOTYPE 2 SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) | PROB(CE) |
|---|---|---|---|---|
| **Treatment-naive, non-cirrhotic** | | | | |
| NT | $33,530 | 10.071 | DOM | 0% |
| PR x 24 | $18,262 | 11.719 | Baseline | 93% |
| SOF + RBV x 12 | $60,699 | 12.030 | EXT DOM | 3% |
| SOF/VEL x 12 | $62,349 | 12.089 | $119,185 vs. PR | 4% |
| **Treatment-naive, cirrhotic** | | | | |
| NT | $83,658 | 7.333 | DOM | 0% |
| PR x 24 | $70,434 | 9.550 | Baseline | 19% |
| SOF + RBV x 12 | $108,778 | 10.291 | DOM | 16% |
| SOF/VEL x 12 | $105,349 | 10.826 | $27,364 vs. PR | 66% |
| **Treatment-experienced, non-cirrhotic** | | | | |
| NT | $36,532 | 9.945 | Baseline | 0% |
| SOF + RBV x 12 | $62,780 | 11.869 | DOM | 27% |
| SOF/VEL x 12 | $62,308 | 12.058 | $12,196 vs. NT | 73% |
| **Treatment-experienced, cirrhotic** | | | | |
| NT | $83,259 | 7.335 | Baseline | 0% |
| SOF + RBV x 12 | $116,856 | 9.484 | DOM | 3% |
| SOF/VEL x 12 | $104,070 | 10.804 | $6,000 vs. NT | 97% |

CE = cost-effectiveness; DOM = dominated; EBR = elbasvir; EXT = extended; GZR = grazoprevir; ICUR = incremental cost-utility ratio; NT = No Treatment; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

**Genotype 3 subgroups**

For genotype 3, the original model results suggest that SOF/VEL will be cost-effective against the comparators presented in three of four subgroups. In the revised results (Table 19), SOF/VEL again appears highly cost-effective in three of four subgroups with likelihoods of cost-effectiveness above 90% in each case and ICURs below $11,000 per QALY.

In the only remaining case (treatment-naive, non-cirrhotic), the manufacturer's results raise doubts regarding the cost-effectiveness of SOF/VEL. In the revised model, PR has a 68% likelihood of being

cost-effective, with SOF/VEL being cost-effective on the other 32% of occasions. The ICUR for SOF/VEL here is around $60,000 per QALY versus PR, which is similar to the results in the manufacturer's analysis.

**TABLE 19: REANALYZED MODEL, GENOTYPE 3 SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) | PROB(CE) |
|---|---|---|---|---|
| **Treatment-naive, non-cirrhotic** | | | | |
| NT | $42,241 | 9.71 | DOM | 0% |
| PR x 24 | $24,089 | 11.41 | Baseline | 68% |
| SOF + RBV x 24 | $122,910 | 11.86 | DOM | 0% |
| SOF + DCV x 12 | $94,005 | 12.04 | DOM | 0% |
| SOF/VEL x 12 | $62,918 | 12.05 | $60,037 vs. PR | 32% |
| EBR/GZR + SOF x 12 | $118,499 | 12.06 | $13,000,183 Vs. SOF/VEL | 0% |
| **Treatment-naive, cirrhotic** | | | | |
| PR x 24 | $83,535 | 7.33 | DOM | 0% |
| SOF + RBV x 24 | $171,573 | 9.96 | DOM | 0% |
| EBR/GZR + SOF x 12 | $163,571 | 10.58 | DOM | 3% |
| SOF/VEL x 12 | $107,378 | 10.64 | $10,949 vs. SOF + DCV | 97% |
| **Treatment-experienced, non-cirrhotic** | | | | |
| NT | $45,189 | 9.57 | Baseline | 0% |
| SOF + RBV x 24 | $131,019 | 11.37 | DOM | 0% |
| SOF/VEL x 12 | $65,519 | 11.88 | $8,803 vs. NT | 94% |
| SOF + DCV x 12 | $95,380 | 11.96 | $370,855 vs. SOF/VEL | 6% |
| **Treatment-experienced, cirrhotic** | | | | |
| NT | $83,249 | 7.33 | Baseline | 0% |
| SOF + RBV x 24 | $176,482 | 9.42 | DOM | 0% |
| SOF/VEL x 12 | $107,579 | 10.50 | $7,680 vs. NT | 100% |

CE = cost-effectiveness; DCV = daclatasvir; DOM = dominated; EBR = elbasvir; EXT = extended; GZR = grazoprevir; ICUR = incremental cost-utility ratio; NT = No Treatment; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

**Genotype 4, 5, 6 subgroups**

As identified above, there is little that can be inferred from comparing results for genotypes 4 and 5/6 against the manufacturer's results because the comparators that can be considered are extremely limited and do not correspond to the manufacturer's reported results. In these cases, the comparisons provided by the "Multiple CEACs" option in the manufacturer's submitted model are between No Treatment and SOF/VEL, and in each case there is a 100% chance of cost-effectiveness for SOF/VEL.

**TABLE 20: REANALYZED MODEL, GENOTYPES 4 AND 5/6 SUBGROUPS**

| TREATMENT | COSTS | QALYS | INCR COSTS | INCR QALYS | ICUR (PER QALY) | PROB(CE) |
|---|---|---|---|---|---|---|
| **Treatment-naive, non-cirrhotic** | | | | | | |
| NT | $33,504 | 10.071 | | | Baseline | 0% |
| SOF/VEL x 12 | $62,459 | 12.080 | $28,955 | 2.008 | $14,417 | 100% |
| **Treatment-naive, cirrhotic** | | | | | | |
| NT | $83,378 | 7.327 | | | Baseline | 0% |
| SOF/VEL x 12 | $105,425 | 10.803 | $22,047 | 3.477 | $6,341 | 100% |
| **Treatment-experienced, non-cirrhotic** | | | | | | |
| NT | $36,586 | 9.939 | | | Baseline | 0% |
| SOF/VEL x 12 | $62,465 | 12.053 | $25,879 | 2.114 | $12,244 | 100% |
| **Treatment-experienced, cirrhotic** | | | | | | |
| NT | $83,429 | 7.325 | | | Baseline | 0% |
| SOF/VEL x 12 | $104,078 | 10.806 | $20,649 | 3.481 | $5,932 | 100% |

CE = cost-effectiveness; ICUR = incremental cost-utility ratio; NT = No Treatment; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

In contrast, while CEAC figures can be generated from the "Run All PSAs" option of the Excel model, these figures cannot be interpreted, as the analysis does not generate expected costs or QALYs, and hence a full incremental analysis is not possible. Given the choice between having either a CEAC for a preferred set of analyses or an incremental analysis, the incremental analysis is preferred.

**Decompensated cirrhosis subgroups**

In the final cases, the SOF/VEL + RBV regimens were compared against LDV/SOF and SOF + RBV in patients with DCC. In both the manufacturer's results and the rerun models (Table 21), SOF/VEL appears to be cost-effective at an indicative threshold of $50,000 per QALY. In these rerun models, the consideration of cost-effectiveness means that No Treatment is compared against SOF/VEL + RBV. In the treatment-naive case, SOF/VEL + RBV again dominates the two other active treatments, but the addition of the No Treatment option provides a more effective comparator — although the SOF/VEL-containing regimen is cost-effective at $32,315 per QALY and hence appears to be cost-effective. In the treatment-experienced case, the original results led to a comparison between LDV/SOF and SOF/VEL + RBV, but the addition of No Treatment removes the former treatment, as it is extendedly dominated. Again, the use of No Treatment as an option allows for clearer identification of cost-effective outcomes, with SOF/VEL + RBV appearing cost-effective at $30,828 per QALY and having an 84% likelihood of cost-effectiveness.

**TABLE 21: REANALYZED MODEL, DECOMPENSATED CIRRHOSIS SUBGROUPS**

| | COSTS | QALYS | ICUR (PER QALY) | PROB(CE) |
|---|---|---|---|---|
| **Treatment-naive** | | | | |
| NT | $76,644 | 2.913 | | 0% |
| SOF + RBV x 48 | $341,310 | 6.625 | DOM | 0% |
| LDV/SOF + RBV x 12 | $220,532 | 7.076 | DOM | 35% |
| SOF/VEL + RBV x 12 | $215,874 | 7.222 | $32,315 vs. NT | 65% |
| **Treatment-experienced** | | | | |
| NT | $76,576 | 2.912 | | 0% |
| SOF + RBV x 48 | $340,328 | 6.627 | DOM | 0% |
| LDV/SOF x 12 | $216,652 | 6.932 | EXT DOM | 16% |
| SOF/VEL + RBV x 12 | $220,603 | 7.584 | $30,828 vs. NT | 84% |

CE = cost-effectiveness; DOM = dominated; EXT = extended; ICUR = incremental cost-utility ratio; LDV = ledipasvir; NT = No Treatment; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; vs. = versus.

# APPENDIX 4: DIFFERENCES BETWEEN THE MANUFACTURER'S PHARMACOECONOMIC REPORT AND RESULTS OBTAINED USING THE SUBMITTED EXCEL MODEL

| MANUFACTURER'S PHARMACOECONOMIC REPORT | EXCEL MODEL |
|---|---|
| Contains No Treatment only in genotype 5/6 submodel. | Contains No Treatment as a comparator in all cases. *No Treatment was found to be relevant in an incremental analysis for several cases in which it was omitted.* |
| States that a justification for monitoring costs is provided in the Excel model. | A set of complicated tables is provided, but there is no clear statement of monitoring costs. |
| Reports on separate models for genotypes 4 and 5/6 | One model is provided for genotype 4/5/6. |
| Reports on separate TN and TE Models. | There is no automatic method of selecting TN or TE subgroups in genotypes 2, 3, or 4/5/6. |
| Both genotype 4 and genotype 5/6 have 4 separate models based on prior exposure (TN/TE) and cirrhosis status (NC/CC). | The combined genotype 4/5/6 can have four separate models based on prior exposure (TN/TE) and cirrhosis status (NC/CC). This requires modification of initial fibrosis distribution. |
| GT4 TN NC Model has comparators EBR/GZR x 12, OMB/PAR/r + RBV x 12, SOF + PR x 12 (Appendix 3-17). | The combined TN NC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. There are no comparators in this analysis that are common with the Pharmacoeconomic Report. |
| GT4 TN CC Model has comparators EBR/GZR R x 12, SOF + PR x 12 (Appendix 3-18). | The combined TN CC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. There are no comparators in this analysis that are common with the Pharmacoeconomic Report. |
| GT4 TE NC Model has comparators EBR/GZR x 12, EBR/GZR + RBV x 16, OMB/PAR/r + RBV x 12, SOF + PR x 12 (Appendix 3-19). | The combined TE NC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. There are no comparators in this analysis that are common with the Pharmacoeconomic Report. |
| GT4 TE CC Model has comparators EBR/GZR x 12, EBR/GZR + RBV x 16, SOF + PR x 12 (Appendix 3-20). | The combined TE CC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. There are no comparators in this analysis that are common with the Pharmacoeconomic Report. |
| GT5/6 TN NC Model has comparators No Treatment and PR (Appendix 3-21). | The combined TN NC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. |
| GT5/6 TN CC Model has comparators No Treatment and PR (Appendix 3-22). | The combined TN CC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. |
| GT5/6 TE NC Model has comparators No Treatment and PR (Appendix 3-23). | The combined TE NC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. |
| GT5/6 TE CC Model has comparators No Treatment and PR (Appendix 3-24). | The combined TE CC model only compares SOF/VEL to No Treatment when the "PSA Multiple Analysis" is run. |

CC = compensated cirrhosis; EBR = elbasvir; GT = genotype; GZR = grazoprevir; NC = non-cirrhotic; OMB/PAR/r = ombitasvir/paritaprevir boosted with ritonavir; PR = pegylated interferon plus ribavirin; PSA = probability sensitivity analysis; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive; VEL = velpatasvir.

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