Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	ledipasvir/sofosbuvir (Harvoni)
Indication	For the treatment of chronic hepatitis C virus (CHC) G1 infection in adults.
Listing request	As per Health Canada indication
Manufacturer	Gilead Sciences Canada, Inc.

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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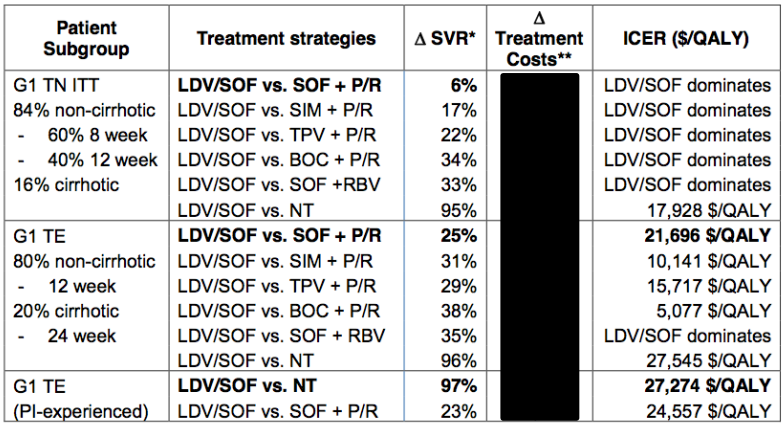
ABBREVIATIONS

BOC	boceprevir
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
G1	genotype 1
HCV	hepatitis C virus
HUI	Health Utilities Index
ICUR	incremental cost-utility ratio
ITT	intention-to-treat population
LDV/SOF	ledipasvir/sofosbuvir
NMA	network meta-analysis
NT	no treatment
Peg-IFN	pegylated interferon
PR	pegylated interferon plus ribavirin
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RNA	ribonucleic acid
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
RBV	ribavirin
TE	treatment-experienced
TN	treatment-naive
TEL	telaprevir

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**LDV/SOF**
Study Question	What is the cost-effectiveness of LDV/SOF versus appropriate comparators — over a lifetime horizon and from a government perspective — in patients with G1 CHC?
Type of Evaluation	Cost-utility analysis
Target Population	Patients with CHC viral infection G1 in the following subgroups: (1) treatment-naive non-cirrhotic; (2) treatment-naive cirrhotic; (3) treatment-experienced non-cirrhotic; (4) treatment-experienced cirrhotic; (5) treatment-experienced with previous exposure to protease inhibitor.
Treatment	LDV/SOF oral for 8, 12, or 24 weeks, depending on patient subgroup.
Outcomes	SVR and QALYs
Comparators	(1) SOF + PR; (2) SIM + PR; (3) TEL + PR; (4) BOC + PR; (5) SOF + RBV; and (6) NT.
Perspective	Government payer
Time Horizon	Lifetime — up to 80 years of age
Results for Base Case	 Source: Manufacturer's pharmacoeconomic submission.[1]
Key Limitations	CDR noted several limitations with the manufacturer's model: 1) Effectiveness estimates were from separate, non-comparative, and likely non-comparable trials. 2) The natural history data for non-cirrhotic to cirrhotic transition appear to be erroneous. 3) Utility estimates were taken from regression models that may not be appropriate. 4) The cost of anemia was likely overestimated. 5) The duration of PR therapy with the SIM + PR regimen was underestimated. 6) The model structure aggregates fibrosis states in early disease. This artificially increases the expected value of eliminating the virus.
CDR Estimate(s)	CDR conducted a number of reanalyses, but was not able to account for all identified limitations. Considerable uncertainty remains in the results. • In treatment-naive and treatment-experienced non-cirrhotic patients, LDV/SOF is likely to remain cost-effective versus comparators.

Patient Subgroup	Treatment strategies	Δ SVR*	Δ Treatment Costs**	ICER ($/QALY)
G1 TN ITT	**LDV/SOF vs. SOF + P/R**	**6%**	[redacted]	LDV/SOF dominates
84% non-cirrhotic	LDV/SOF vs. SIM + P/R	17%		LDV/SOF dominates
- 60% 8 week	LDV/SOF vs. TPV + P/R	22%		LDV/SOF dominates
- 40% 12 week	LDV/SOF vs. BOC + P/R	34%		LDV/SOF dominates
16% cirrhotic	LDV/SOF vs. SOF +RBV	33%		LDV/SOF dominates
	LDV/SOF vs. NT	95%		17,928 $/QALY
G1 TE	**LDV/SOF vs. SOF + P/R**	**25%**		**21,696 $/QALY**
80% non-cirrhotic	LDV/SOF vs. SIM + P/R	31%		10,141 $/QALY
- 12 week	LDV/SOF vs. TPV + P/R	29%		15,717 $/QALY
20% cirrhotic	LDV/SOF vs. BOC + P/R	38%		5,077 $/QALY
- 24 week	LDV/SOF vs. SOF + RBV	35%		LDV/SOF dominates
	LDV/SOF vs. NT	96%		27,545 $/QALY
G1 TE	**LDV/SOF vs. NT**	**97%**		**27,274 $/QALY**
(PI-experienced)	LDV/SOF vs. SOF + P/R	23%		24,557 $/QALY

[redacted]	• In treatment-experienced cirrhotic patients, ICURs of LDV/SOF versus SOF + PR were consistently greater than $50,000 per QALY, with the probability of the ICUR being < $50,000 per QALY at less than 30%. ICUR of LDV/SOF versus SIM + PR went up to $36,000 per QALY. CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

BOC + PR = boceprevir plus pegylated interferon plus ribavirin; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; G1 = genotype 1; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; LDV/SOF = ledipasvir/sofosbuvir; NT = no treatment; QALY = quality-adjusted life-year; RBV = ribavirin; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin; SOF + RBV = sofosbuvir plus ribavirin; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive; TEL + PR = telaprevir plus pegylated interferon plus ribavirin.

EXECUTIVE SUMMARY

Background

Ledipasvir/sofosbuvir (LDV/SOF) (Harvoni) is a dual-therapy single tablet taken daily for the treatment of chronic hepatitis C virus (CHC) genotype 1 infection in adults.[2] It is administered for eight, 12, or 24 weeks depending upon treatment experience (naive or experienced, the latter being defined as having failed prior therapy with an interferon-based regimen, including regimens containing a hepatitis C virus [HCV] protease inhibitor); the presence or absence of cirrhosis; and viral load (eight-week treatment can be considered only in treatment-naive patients without cirrhosis who have pre-treatment HCV ribonucleic acid [RNA] less than 6 million IU/mL).[2] The manufacturer submitted a confidential price of [redacted] per 90 mg/400 mg tablet, which corresponds to a price of [redacted] for eight weeks' therapy; [redacted] for 12 weeks' therapy; and [redacted] for 24 weeks' therapy.

The manufacturer is seeking reimbursement in line with the Health Canada indication.

The manufacturer submitted a cost-utility analysis conducted over a patient lifetime (up to 80 years of age) from a government-payer perspective. The manufacturer's base-case analyses compared LDV/SOF with six comparators: sofosbuvir plus pegylated interferon plus ribavirin (SOF + PR); simeprevir plus pegylated interferon plus ribavirin (SIM + PR); telaprevir plus pegylated interferon plus ribavirin (TEL + PR); boceprevir plus pegylated interferon plus ribavirin (BOC + PR); sofosbuvir plus ribavirin (SOF + RBV); and no treatment (NT).[1] The model uses a simplified version of one originally developed by Grieve et al. (2006)[3] and updated by Grishchenko et al. (2009).[4] The base-case analyses examined the cost-effectiveness of LDV/SOF in mixed patient and treatment populations. The treatment-naive cohort was composed of 84% non-cirrhotic patients (of whom 60% received eight weeks of therapy and 40% received 12 weeks of therapy) and 16% cirrhotic patients, all of whom received 12 weeks of therapy.

In the base-case analyses, the manufacturer reported that LDV/SOF was dominant compared with all treatments in the treatment-naive analyses, except when compared with no treatment, for which the incremental cost-utility ratio (ICUR) is estimated to be $17,928 per quality-adjusted life-year (QALY) gained. In treatment-experienced (TE) patients, LDV/SOF dominated SOF + RBV. The ICURs for LDV/SOF compared with all other comparators are less than $30,000 per QALY. The ICURs for LDV/SOF in protease inhibitor-failed patients are also less than $30,000 per QALY.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations in the submitted model:

1. The effectiveness parameters used in the model are drawn from non-comparative trials.
2. The model structure interacts with the natural history parameters to create an error. The transition rates combine data for mild and moderate states into a single non-cirrhotic state. To use the Grishchenko[4] data as reported would require time-dependent or cycle-specific transition rates.
3. The cost of anemia is likely overestimated, which will favour LDV/SOF (the incidence of anemia is 0.5% with LDV/SOF compared with 9% to 50% with comparators).
4. For the SIM + PR regimen, the manufacturer assumed that the average duration of PR (used to calculate drug costs) would vary between 35 and 36 weeks for both treatment-naive and TE patients. This may overestimate the cost of the SIM + PR regimen in treatment-naive patients and those with prior relapse, as evidence from clinical trials suggests the majority of these patients would be eligible for 24 weeks' duration of PR.
5. The utility parameters might not be reliable.

6. The probabilistic sensitivity analysis (PSA) was incorrectly implemented; it used an insufficient number of simulations (1,000) to produce stable estimates of the expected costs and QALYs for each intervention, and lacked robust descriptions of the uncertainty regarding the expected values.
7. The model structure is aggregating states (fibrosis stages) in early disease that, while having equivalent quality-of-life weights, have very different costs of care, with the effect of increasing the expected cost of care for early disease compared with a model that kept the mild and moderate states separate. This artificially increases the expected value of eliminating the virus.

Conclusions

Given the high sustained virologic response (SVR) rates observed with LDV/SOF, it is unsurprising that in non-cirrhotic patients, CDR reanalyses find it is still likely to be cost-effective. Intuitively, it is unlikely that a *de novo* model that resolved the many faults with the submitted analysis would arrive at a different conclusion; however, on balance, CDR considers that these results are likely an underestimate of the actual ICUR of LDV/SOF versus other comparators.

In TE cirrhotic patients, ICURs of LDV/SOF versus SOF + PR were consistently greater than $50,000 per QALY, with the probability of the ICUR being < $50,000 per QALY at less than 30%. An ICUR of LDV/SOF versus SIM + PR went up to $36,000 per QALY. The estimates of the cost-effectiveness of LDV/SOF in cirrhotic TE patients are similarly limited by the flaws in the submitted model, and even CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

REVIEW OF 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 nine states. Two states deal with non-cirrhotic disease (chronic hepatitis C [CHC] non-cirrhotic and sustained virologic response [SVR] non-cirrhotic); three states deal with cirrhotic disease (compensated cirrhosis, decompensated cirrhosis, and SVR cirrhotic); three states deal with cirrhosis complications (hepatocellular carcinoma, liver transplant, and post-liver-transplant). The final state is death. Note that the model does not have states for screening and diagnosis; nor does it have a reinfection state.[1]

The model structure is a simplification of the Shepherd et al.[5] model, which had considerably more non-cirrhotic states. The natural history transition rates are based upon a number of different studies — Grishchenko,[4] Fattovitch, Shepherd,[5] and Cardoso.[6] The effectiveness data are taken from the active groups of the pivotal trials for the six therapies being evaluated. For patients with prior failure to a protease inhibitor (PI), SVR rates from the subgroup of patients experienced to a protease inhibitor in ION-2 and the abstract from Pol et al.[7] were used for ledipasvir/sofosbuvir (LDV/SOF) and sofosbuvir plus pegylated interferon plus ribavirin (SOF + PR), respectively. In an alternate analysis, results from a manufacturer-conducted, unpublished network meta-analysis (NMA)[8]are used to inform comparative effectiveness in treatment-naive patients. Utility data (Health Utilities Index Mark 2 [HUI2] and Mark 3 [HUI3]) are taken from two relatively recent published surveys of a Canadian CHC population (Hsu 2012[9] and John-Baptiste 2009[10]). These appear to report companion studies, as they are from the same research team and use the same measures. Resource utilization is based on clinical trial observations, clinical experts' assumptions, and the literature. Costs are taken from Ontario health care cost sources.

The patient cohort is assumed to have a mean age of 45 at the start of the model and is followed up to 80 years of age. The cohort consists of a mixture of cirrhotic and non-cirrhotic patients and separate analyses are undertaken for treatment-naive (TN), treatment-experienced (TE), and PI failure patients. The TE cohort does not differentiate by type of prior response; non-responders (null responders), prior relapsers, and breakthrough patients are pooled together as a single group. Pairwise analyses are reported for three LDV/SOF treatment regimens (eight, 12, and 24 weeks) against each of six comparators:

- SOF + PR
- Simeprevir plus pegylated interferon plus ribavirin (SIM + PR)
- Telaprevir plus pegylated interferon plus ribavirin (TEL + PR)
- Boceprevir plus pegylated interferon plus ribavirin (BOC + PR)
- Sofosbuvir plus ribavirin (SOF + RBV)
- No treatment.

Comparisons of alternative LDV/SOF regimens are not reported. The format in which the results are presented does not allow the assessment of the cost-effectiveness of 12 weeks' LDV/SOF compared with eight weeks' LDV/SOF in TN non-cirrhotic patients.

2. MANUFACTURER'S BASE CASE

Table 2 summarizes the manufacturer's base-case analyses of the cost-effectiveness of different LDV/SOF therapies in mixed patient populations.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Patient Subgroup	Treatment strategies	Δ SVR*	Δ Treatment Costs**	ICER ($/QALY)
G1 TN ITT	**LDV/SOF vs. SOF + P/R**	**6%**	[redacted]	LDV/SOF dominates
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- 24 week	LDV/SOF vs. SOF + RBV	35%		LDV/SOF dominates
	LDV/SOF vs. NT	96%		27,545 $/QALY
G1 TE	**LDV/SOF vs. NT**	**97%**		**27,274 $/QALY**
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BOC + PR = boceprevir plus pegylated interferon plus ribavirin; G1 = genotype 1; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; LDV/SOF = ledipasvir/sofosbuvir; NT = no treatment; QALY = quality-adjusted life-years; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive; TEL+ PR = telaprevir plus pegylated interferon plus ribavirin.
Source: Manufacturer's pharmacoeconomic submission, p.4.[1]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

3.1 Deterministic Sensitivity Analyses

The deterministic sensitivity analyses reported examined the outcomes of:

- Varying the SVR rate for LDV/SOF over the observed 95% confidence interval (CI)
- Varying the percentage of cirrhotics in the combined population by ± 25%
- Varying the incidence of adverse effects by ± 25%
- Varying health state costs by ± 25%
- Varying health state utilities by ± 25%
- Varying transition probabilities by ± 25%
- Varying background mortality rates by ± 25%
- Applying a discount rate of 0 and 3%.

For the treatment-naive patient group, the manufacturer reports that LDV/SOF continued to dominate SOF + PR in all deterministic sensitivity analyses.

For the treatment-experienced patient group, none of the resulting ICURs exceeded $50,000 per quality-adjusted life-year (QALY).

3.2 Probabilistic Sensitivity Analyses

The probabilistic sensitivity analysis (PSA) applied beta and gamma distributions to health state utilities and costs, transition probabilities, and SVR rates. For the utilities distributions, these were assumed rather than based upon the information reported in the literature.

- For the treatment-naive patient group, the manufacturer reported that the probability of LDV/SOF being dominant over SOF + PR was 100%.
- For the TE patient group comparison with SOF + PR, the manufacturer reported a 96% probability that the incremental cost-utility ratio (ICUR) would be less than $50,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The CADTH Common Drug Review (CDR) identified a significant number of major problems with the submitted analyses, which are identified and explained below. 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. This was beyond the scope of the evaluation.

- **The effectiveness parameters used in the model are drawn from non-comparative trials.** The SVR rates used in the model are taken from the active groups of the relevant comparator trials. 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 the differential effectiveness used in the model accurately captured the magnitude of the incremental benefit of LDV/SOF. The manufacturer submitted an alternate analysis based upon a non-standard NMA. CDR concluded that the alternative effectiveness estimates were problematic and should be interpreted with caution (see Appendix 6, in the CDR Clinical Review). In addition, the use of the NMA did not address the substantial structural problems with the cost-effectiveness analyses, and CDR analyses using the NMA would not be informative.

- **The model structure interacts with the natural history parameters to create an error.** The transition rates combine data for mild and moderate states into a single non-cirrhotic state. To use the Grishchenko data as reported would require time-dependent or cycle-specific transition rates. The manufacturer states that the transition rate for the non-cirrhotic to cirrhotic state is based upon Grishchenko et al.[4] In the Grishchenko paper, the non-cirrhotic state consists of mild and moderate CHC. Combining the transition rates for these two states into a single state should not lead to a constant transition rate, as the manufacturers report. The combination of the mild and moderate non-cirrhotic states in the model structure serves no analytical purpose while introducing the potential for error into the results by using transition data that are based upon the specification of mild and moderate states. An illustration of the impact of combining the transition probabilities from Grishchenko et al. is provided in Appendix 3 (Manufacturer's Key Assumptions).

- **The utility parameters might not be reliable.** The utility data are drawn from two studies: Hsu et al. 2012[9] and John-Baptiste et al.[10] Specifically, utilities are taken from regression models that attempt to predict utility measured using the HUI2 with clinical stage of disease and personal characteristics as the independent variables. The main health state utilities are taken from Hsu et al.[9] In their regression model, the authors regress HUI2 on the following variables: disease stage, treatment, viral clearance, cirrhosis, hepatocellular carcinoma, transplantation, age, education, marital status,

income, and comorbidity. Of these, viral clearance, transplantation, marriage, income, and comorbidities reach statistical significance. Given the inclusion of parameters that are not statistically significantly different from 0 in the model, and the possibility of correlation between some of the significant and non-significant variables, the predicted health state values from the regression model might not be reliable. Further, the descriptive statistical mean values vary significantly according to characteristics — such as marriage, income, and education — for which the data sample is unlikely to be representative of the population that will be affected by the decision the model is designed to inform.

A similar problem applies to the utility increment for the SVR state, which is taken from the John-Baptiste et al. study.[10] The value (0.08) is taken from the HUI3 model rather than the HUI2 model. For this model, HUI3 utility is regressed on SVR, age, gender, education, Charlson Score, and comorbidities. The model reports parameter values and CIs rather than significant values. However, where the CI includes 0, the interpretation is the same as the coefficient being not statistically significantly different from 0. Seven out of the 11 independent variables have coefficients with a CI that crosses 0. Again, given the inclusion of parameters that are not statistically significantly different from 0 and the potential correlation between parameters, we cannot rely on the predicted values from this model; nor can we use the descriptive means, as we know that mean values vary by case-mix characteristics, and the study sample is unlikely to be representative of the population that will be affected by the decision the model is designed to inform.

- **The cost of anemia is likely overestimated.** The duration and cost associated with the management of anemia secondary to treatment will likely depend on the duration of exposure to PR. The study used by the manufacturer (Lachaine et al.[11]) to estimate the cost of treatment-induced anemia was conducted from 2007 to 2012 (prior to the introduction of SIM and SOF) and included 95.2% of patients treated with PR only. This means that the duration of PR exposure (and associated anemia and costs) was longer (48 weeks) than what is likely to be observed in current practice, due to shorter duration of PR and response-guided therapy. Further, the manufacturer assumed that 25% of patients with anemia would require erythropoietin, while the abstract by Lachaine et al. reports that 17.7% of patients required erythropoietin.[11] This is likely overestimated, as reducing the dose of ribavirin (RBV) is often sufficient to control anemia.[12] The overestimation of the cost of anemia will favour LDV/SOF (the incidence of anemia is 0.5% with LDV/SOF compared with 9% to 50% with comparators).

- **Overestimation of SIM + PR cost in treatment-naive and prior relapsers:** For the SIM + PR regimen, the manufacturer assumed that the average duration of PR (used to calculate drug costs) would vary between 35 and 36 weeks for both treatment-naive and treatment-experienced patients. This may overestimate the cost of the SIM + PR regimen in treatment-naive patients and those with prior relapse, as evidence from clinical trials suggests the majority of these patients would be eligible for a 24-week duration of PR.[13]

- **The format in which the results are presented does not allow the assessment of the cost-effectiveness of 12 weeks compared with eight weeks of LDV/SOF in treatment-naive non-cirrhotic patients who have pre-treatment hepatitis C virus (HCV) ribonucleic acid (RNA) less than 6 million IU/mL.** The incremental cost for 12 weeks of LDV/SOF compared with no treatment is estimated to be [redacted]; the same figure for eight weeks of LDV/SOF is [redacted], indicating that four weeks of additional LDV/SOF has a net cost of [redacted]. The manufacturer indicates that the incremental SVR is 94% for eight weeks and 97% for 12 weeks. The ICURs for 12- and eight-week

LDV/SOF versus no therapy are reported to be $29,330 and $17,953 per QALY, respectively. There is a 3.2% premium in the SVR rate for 12 weeks over eight weeks LDV/SOF compared with a 49% premium in cost. Without the incremental QALY data, it is not possible to identify the implied ICUR for 12 weeks compared with eight weeks, but these figures suggest is it highly unlikely to be cost-effective. Unfortunately, the executable model provided does not, as far as CDR reviewers can establish, allow the comparison of the two LDV/SOF treatment strategies.

- **The reported ICURs are likely to be biased due to being calculated using the deterministic parameter values rather than the expected values from the probabilistic analysis outputs.** On examination of the executable model, it became clear that the ICURs reported as the base-case results were calculated using the deterministic model results rather than the outputs of the probabilistic analysis. This is problematic as it assumes that the model is linear. When the value for one parameter is set at its mean (expected value), all other parameters would be expected to take their mean value. However, when models include parameters that do not have particular symmetrical distributions, which is often the case for costs and utilities, this assumption is unlikely to hold. The effect is that the analysis forces parameters to take on combinations of values that are unlikely to be observed in practice, hence the results from the model are unlikely to reflect what we would expect to observe in practice. Best practice requires that ICURs are calculated using the means of the costs and outcomes produced by the probabilistic analyses, as well-conducted PSAs will account for any asymmetrical distributions by running sufficient simulations for the estimation of stable means for the cost and outcome distributions.

- **The PSA appears not to have respected the logical ordering of health state values, creating the possibility that some simulations will have irrational results — e.g., where the utility for the transplant state is higher than the utility for the SVR state**. In CHC, there is a logical ordering to the utility weights for some of the states — particularly non-cirrhotic disease, cirrhotic disease, and decompensated cirrhotic disease. When running a PSA, it is important to ensure that simulations respect this ordering. Failure to do this will result in incorrect results for some simulations, which will lead to a misspecification of the mean utility for each intervention in the probabilistic analysis, leading in turn to incorrect probabilistic ICURs. The greater the uncertainty around the mean utility weight, the greater the chance that illogical utilities will have been sampled in the absence of "hardwiring" the logical ordering using utility decrements rather than mean utilities. The report tells us only that the utility distributions were based upon published mean values and assumptions; hence, we cannot assess the impact of this error on the probabilistic model results.

- **The PSA uses an insufficient number of simulations (1,000) to produce stable estimates of the expected costs and QALYs for each intervention or robust descriptions of the uncertainty around the expected values.** When sampling from probability distributions in order to estimate the mean values for costs and outcomes, it is important to run sufficient simulations to ensure that all possible combinations of values on the input distributions are sampled sufficiently frequently that additional simulations will not impact the expected value 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 indicate that more than 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 and providing no 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.

- **The model structure aggregates states (fibrosis stages) in early disease that, while having equivalent quality of life weights, can have very different costs of care.** This will increase the expected cost of care for early disease compared with a model that keeps the mild and moderate states separate. This artificially increases the expected value of eliminating the virus. Previous studies of the cost-effectiveness of CHC treatments that have used mild and moderate CHC as separate disease states indicate a substantial difference in the costs of care. Grishchenko, for example, reports that the cost of care for moderate disease is nearly three times the cost for mild disease. Hence, when combining these two states into a single state, the proportion of patients that are assumed to have mild versus moderate disease is an important determinant of the appropriate expected cost to be used in the model for the combined state. In the absence of good data on this proportion for the Canadian population, the effect of combining the two states carries a substantial risk that the monetary savings associated with moving from chronic but non-cirrhotic CHC to SVR will be overstated, leading to biased estimates of the cost-effectiveness of all the therapies, and the bias would be greater for the more effective therapies.

- **The analyses assume 100% compliance with LDV/SOF but not with other CHC therapies**. This is inconsistent with the literature on compliance with self-administered oral medications, and has the effect of biasing the results in favour of LDV/SOF. The evidence on compliance with oral self-administered treatment is that non-compliance continues to be a significant issue even with life-threatening diseases such as HIV/AIDS. The assumption of 100% compliance for LDV/SOF is not credible. The effect of less than 100% compliance would be to reduce the effectiveness — as indicated by the comparison of eight- and 12-week treatment regimens — with an uncertain impact on the costs of treatment. If the treatment is paid for all at once, then there would be no cost savings associated with non-compliance. However, if the treatment was paid for on a weekly or monthly basis, then the costs would be correspondingly reduced. The impact on the expected cost-effectiveness of LDV/SOF would depend upon the interaction of the degree of non-compliance, the magnitude of the effectiveness penalty due to non-compliance, and the degree to which non-compliance translated into reduced prescription costs. The failure to allow any degree of non-compliance means that provided cost-effectiveness estimates are likely to be both inaccurate and unduly precise — even if all the other concerns are remedied.

5. CADTH COMMON DRUG REVIEW ANALYSES

Many of the concerns detailed above cannot be addressed by simply correcting the parameter values used, as they are driven by structural problems with the model or fundamental problems with the evidence base. However, CDR performed a number of reanalyses, in which CDR reviewers corrected the mistakes with regard to the calculation of the ICUR by using the outputs of the PSA. CDR also increased the number of simulations to 20,000 to provide confidence that the means and standard errors of the output distributions were stable.

The following reanalyses were performed:

- Exploration of the uncertainty with SVR rates in TE cirrhotic patients due to small sample size in the ION-2 trial
- Alternative utility values (HUI3 from Chong 2003[14])
- Reduced cost of anemia: CDR will assign a cost of anemia that is 12.5% of the cost reported in Lachaine et al.[11](0.125 × $10,787 = $1,348.38) instead of the $2,696.85 used by the manufacturer
- Proportion of patients eligible for short duration of PR based on response-guided therapy (RGT) in the SIM + PR group: the manufacturer assumed 41% and 52% of patients would receive PR for 24 and 48 weeks, respectively, which results in an average duration (used to calculate costs of PR) of 36 weeks. To account for the treatment-naive and prior-relapse patients eligible for 24 weeks of PR (ranging from 79% to 93% of patients), CDR will assume a revised duration for PR of 26 weeks instead of 36 weeks.

CDR undertook the analyses to examine the cost-effectiveness of LDV/SOF for 24 weeks in TE cirrhotic patients, as the cost of LDV/SOF for these patients is [redacted] and the evidence for effectiveness is based upon only 22 patients from the ION-2 trial. CDR therefore considered that this was a particularly uncertain and high-budget impact indication. CDR also ran analyses for the TE non-cirrhotic patient group and the TE pegylated interferon (Peg-IFN) group.

Due to time constraints, CDR limited the reanalyses to the comparison of LDV/SOF with SOF + PR and SIM + PR. The rationale was that CADTH 2014 Recommendations for Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1[15] recommended the use of SIM daily for 12 weeks, in combination with PR for 24 to 48 weeks, as the PI of choice for treatment-naive patients or for treatment-experienced patients with prior relapse. SOF + PR, although still under review by most drug plans, is the regimen most similar to LDV/SOF.

5.1 Exploration of the uncertainty with SVR rates in TE cirrhotic patients due to small sample size

Among the 22 patients for whom LDV/SOF report data from ION-2, all patients achieved SVR, leading to an SVR rate of 100% with LDV/SOF. SVR rates were lower with SOF + PR (71.2%) and SIM + PR (54.2%), but based on a larger sample size (N = 52 and N = 24, respectively). In order to capture the uncertainty associated with the small number of observations within the probabilistic analysis, CDR defined the SVR probability as a beta (21.9, 0.01).

As shown in Appendix 3, Figure 4, CDR plotted two alternative beta distributions for LDV/SOF. The first assumes that a hypothetical 23rd patient was a non-responder (green plot: LDV/SOF 22/1); the second assumes that two additional patients did not respond (blue plot: LDV/SOF 22/2). It is clear that two additional data points could radically change the relative advantage of LDV/SOF compared with the alternative therapies (there would be more overlap between LDV/SOF and SOF + PR, SIM + PR) in terms of SVR rates.

5.2 CDR analysis using alternate utility values, lower anemia cost, and shorter duration of PR in the SIM + PR group

Table 3 presents the results of CDR reanalyses using the combination of utility values from Chong et al.,[14] lower anemia cost, and shorter duration of PR in the SIM + PR group. Results of the reanalyses in which these parameters were changed individually are presented in Appendix 3.

TABLE 3: CDR REANALYSIS USING ALTERNATE UTILITY VALUES, LOWER ANEMIA COST, AND SHORTER DURATION OF PEGYLATED INTERFERON PLUS RIBAVIRIN IN THE SIM + PR GROUP

	Absolute		Incremental Analysis			
	Costs	**QALYs**	**Costs**	**QALYs**	**ICUR**	**% ICUR < $50K per QALY**
Genotype 1, Treatment-Experienced Non-Cirrhotic						
LDV/SOF (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	$16,562	100%
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
SIM + PR	$50,741	12.17	Baseline treatment			
Genotype 1, Treatment-Experienced Cirrhotic						
LDV/SOF (24 weeks)	$139,860	11.31	$47,242	0.79	$59,538	29%
SOF + PR (12 weeks)	$92,618	10.52	Baseline treatment			
SIM + PR	$95,306	10.08	Dominated by SOF + PR			
Genotype 1, Treatment PI + PR Failures						
LDV/SOF (12 weeks/24 weeks cirrhotics)	[redacted]	[redacted]	[redacted]	[redacted]	$40,389	NA
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
No treatment	$23,673	11.01	Baseline treatment			

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

Note that the central estimates for the TE cirrhotic patients are consistently not cost-effective at a $50,000 per QALY threshold compared with SOF + PR. Compared with SIM + PR, the ICUR for LDV/SOF is $36,223 per QALY. The ICURs for LDV/SOF versus SIM + PR and SOF + PR in the TE non-cirrhotic and the PI failure patient groups are cost-effective.

The second notable feature is the lack of impact of the change in the costs of anemia. The halving of a cost that affects between 16% and 20% of patients should have an impact on the expected costs for SIM + PR and SOF + PR, yet the estimated costs for both interventions are effectively identical to the base-case costs. This raises the concern that there continue to be problems with the coding of the model that mean these changes are not actually being applied to the calculations.

5.3 Price Reduction Scenario

For patient groups in whom LDV/SOF was not cost-effective, CDR also conducted an analysis of the price required to achieve an ICUR below $50,000 per QALY.

TABLE 4: PRICE REDUCTION SCENARIOS

Genotype 1, Treatment-Experienced Cirrhotic						
		Absolute		Incremental Analysis		
		Costs	QALYs	Costs	QALYs	ICUR
Submitted Price [redacted]	LDV/SOF (24 weeks)	$139,860	11.31	$47,242	0.79	$59,538
	SOF + PR (12 weeks)	$92,618	10.52	Baseline treatment		
7% Price Reduction [redacted]	LDV/SOF (24 weeks)	$132,084	11.32	$39,615	0.79	$50,179
	SOF + PR (12 weeks)	$92,469	10.53	Baseline treatment		
7.5% Price Reduction [redacted]	LDV/SOF (24 weeks)	$131,851	11.32	$39,409	0.80	$49,548
	SOF + PR (12 weeks)	$92,442	10.52	Baseline treatment		
25.6% Price Reduction [redacted]	LDV/SOF (24 weeks)	$112,272	11.30	$19,852		
	SOF + PR (12 weeks)	$92,420	10.51	Baseline treatment		
25.8% Price Reduction [redacted]	LDV/SOF (24 weeks)	$111,856	11.31	$19,688		
	SOF + PR (12 weeks)	$92,188	10.52	Baseline treatment		
25.6% Price Reduction [redacted]	LDV/SOF (24 weeks)	$112,272	11.30	$19,852		
	SOF + PR (12 weeks)	$92,420	10.51	Baseline treatment		

ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; QALY = quality-adjusted life-years; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

Of note, due to the several structural limitations to the model for which CDR could not account in its reanalyses, the scale of price discounts required to achieve cost-effectiveness in the TE cirrhotic subgroup in the real world may be greater than those indicated by the price threshold analyses presented in Table 4.

6. ISSUES FOR CONSIDERATION

The patient population the model considers is those patients who are currently suitable for and willing to undergo standard care, including PR or RBV. There are four categories of patients for whom LDV/SOF may be suitable and for whom the suggested indication might be covered, but they are not considered in this model: (a) diagnosed patients whom clinicians will not treat with current therapies; (b) diagnosed patients who choose not to be treated with current therapies; (c) undiagnosed patients identified through opportunistic case-finding strategies; and (d) undiagnosed patients identified through screening programs. The model structure, case mix, cost, and health gain information for these patient groups are likely to be systematically different from the information in the model.

The indication for LDV/SOF is for CHC independent of disease stage. Hence, the requirement for clinical assessment to qualify for treatment will simply be confirmation of CHC, and allowing sufficient time to ensure that any spontaneous sustained viral response is achieved and thus all treated patients have CHC. The ease of administration and low adverse event burden associated with LDV/SOF means CHC is now likely to meet the Wilson and Jungner criteria[16] for supporting the introduction of screening. Patients identified via screening are likely to differ from the currently identified CHC population in a number of ways. They are likely to have a different age profile, be distributed differently over the disease course, and be at lower risk of comorbidities. The presence of comorbidities would likely have led to opportunistic identification of carrier status as the comorbid conditions were treated. Therefore, the states, utilities, and the transition probabilities used in the submitted model cannot be assumed to be appropriate for currently unidentified patients. Similar considerations apply to patients identified through active case-finding strategies that fall short of a formal screening program.

At the other end of the case-mix spectrum, patients whose clinicians are currently cautious about treating with the standard therapies are likely to have very different disease profiles than that used in the model. Concern over current therapies may be driven by an assessment of the patients' ability to withstand the treatment burden; hence, they are arguably a more sickly, more advanced patient group, with less ability to benefit from achieving SVR than is assumed in the submitted model. Hence, the model is likely to systematically misstate the cost-effectiveness of therapy for these patients.

Similarly, patients who choose not to use current therapies even though their clinicians would support their use are making some assessment about the balance of risks and expected benefits from therapy. It is credible that these patients consider the current burden of disease too low to justify the burden of the standard therapies. In that case, these patients would have a different disease progression trajectory (and hence magnitude of benefit) from those patients considered in the model. Again, the cost-effectiveness estimates produced by the current model are likely to systematically misstate the value of these therapies in this last patient group.

In summary, it is important to understand that the submitted analysis does not speak to the cost-effectiveness of LDV/SOF in conceivable patient groups, but only in those patients whom clinicians consider suitable candidates for standard therapies and who are willing to undergo them.

7. PATIENT INPUT

Input was received from six patient groups: the Canadian Liver Foundation (CLF), the Gastrointestinal (GI) Society, the Canadian Treatment Action Council (CTAC), the Pacific Hepatitis C Network, the Hepatitis C Education and Prevention Society (HepCBC), and the Centre d'Aide aux Personnes Atteintes d'Hépatite C (CAPAHC).

Patient groups noted that adverse effects with current therapy can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, headaches, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some triple-therapy regimens require patients to take up to 20 pills throughout the day, with specific food requirements, and have adverse drug interactions with antiretroviral therapies. Many patients have contraindications or cannot tolerate interferon, and thus are ineligible for interferon-based regimens. Injections associated with interferon can be a triggering factor and source of anxiety for those with a history of injection drug use. Those who have failed interferon-based treatments have few treatment options. Patient groups considered that

LDV/SOF offers advantages over current treatments, including that it requires just one pill a day with no stringent food requirements; it is interferon-free; and treatment is required for only eight to 12 weeks, further minimizing potential side effects. Decreasing treatment time is a priority for patients and health care providers due to its impact on adherence and the burden of side effects, and to expedite patients' return to their normal lives.

Duration of therapy, compliance, and risk of specific adverse effects (anemia, depression, rash) were considered in the economic model submitted by the manufacturer. However, there is a lack of good, real-life evidence on costs and disutility associated with adverse effects; and comparative real-life compliance with LDV/SOF versus other direct-acting antivirals is unknown.

8. CONCLUSIONS

Given the high SVR rates observed with LDV/SOF, it is unsurprising that in non-cirrhotic patients, CDR reanalyses find it is still likely to be cost-effective. Intuitively, it is unlikely that a *de novo* model that resolved the many faults with the submitted analysis would arrive at a different conclusion, but on balance, CDR considers that these results are likely to be an underestimate of the actual ICUR of LDV/SOF versus other comparators.

In TE cirrhotic patients, ICURs of LDV/SOF versus SOF + PR were consistently greater than $50,000 per QALY, with the probability of the ICUR being < $50,000 per QALY at less than 30%. ICUR of LDV/SOF versus SIM + PR went up to $36,000 per QALY. The estimates of the cost-effectiveness of LDV/SOF in cirrhotic TE patients are similarly limited by the flaws in the submitted model, and even CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

APPENDIX 1: COST COMPARISON

The comparators presented in the following table have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified.

Existing product listing agreements are not reflected in the table, and as such, may not represent the actual costs to public drug plans.

TABLE 5: COST COMPARISON TABLE FOR DRUGS FOR CHRONIC HEPATITIS C, GENOTYPE 1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost For 1 Course Of Therapy ($)	Cost For 1 Course Of Combo Therapy ($)
LDV/SOF	**90 mg / 400 mg**	**Tab**	[redacted][a]	**90 mg/ 400 mg once daily**	**8 to 24 weeks**[b]	[redacted] **(8 weeks)** [redacted] **to** [redacted] **(12 to 24 weeks)**	[redacted] **(8 weeks)** [redacted] **to** [redacted] **(12 to 24 weeks)**
Direct-acting antivirals in combination with pegylated interferon alfa plus ribavirin therapy							
Sofosbuvir (Sovaldi) plus Peg-IFN + RBV	400 mg	Tab	[redacted][a]	400 mg once daily	12 weeks[e]	[redacted]	[redacted]
	180 mcg/ 200 mg	Vial/tabs	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	12 weeks	4,750	
Sofosbuvir (Sovaldi) + RBV	400 mg	Tab	[redacted][a]	400 mg once daily	24 weeks[f]	[redacted]	[redacted] to [redacted]
	400 mg 600 mg	Tab	14.5000[f,g] 21.7500[f,g]	1,000 to 1,200 mg daily	24 weeks	6,090 to 7,308	
Simeprevir (Galexos) plus Peg-IFN + RBV	150 mg	Cap	434.5500[c]	150 mg once daily	12 weeks	36,502	46,002 to 55,502
	180 mcg/ 200 mg	Vial/tabs	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	
Telaprevir (Incivek) plus Peg-IFN + RBV	375 mg	Tab	69.3810	3 x 375 mg two times daily	12 weeks	34,968	44,468 to 53,968

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost For 1 Course Of Therapy ($)	Cost For 1 Course Of Combo Therapy ($)
	180 mcg/ 200 mg	Vial/tabs	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	
Boceprevir (Victrelis) plus Peg-IFN + RBV	200 mg	Cap	12.5000	4 x 200 mg three times daily	24 to 44 weeks	25,200 to 46,200	37,365 to 67,055
	120 mcg/ 200 mg	Pens/ caps	868.9600	Peg-IFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day	28 to 48 weeks	12,165 to 20,855	
Boceprevir and Peg-IFN alfa-2b + RBV (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 caps+ 2 pens+ 56 caps	2652.55[g] 2652.55[g] 2726.00[g] 2726.00[g]	Boceprevir 800 mg three times daily; Peg-IFN 1.5 mcg/kg/ week; RBV 800 to 1,400 per day	24 to 44 weeks	31,831 to 59,972	31,831 to 59,972
Pegylated interferon alfa plus ribavirin therapy							
Peg-IFN alfa-2a plus RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or syringe/ 28 tabs 35 tabs 42 tabs	395.8400	Peg-IFN 180 mcg/week; RBV 800 to 1,200 mg/day	24 to 48 weeks	9,500 to 19,000	9,500 to 19,000
Peg-IFN alfa-2b plus RBV (Pegetron)	50 mcg/ 200 mg	2 vials + 56 caps	786.3900	Peg-IFN 1.5 mcg/kg/ week; RBV 800 to 1,400 mg/day	24 to 48 weeks	9,437 to 18,873	9,437 to 18,873
	150 mcg/ 200 mg	2 vials + 84 or 98 caps	868.9600			10,428 to 20,855	10,428 to 20,855

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost For 1 Course Of Therapy ($)	Cost For 1 Course Of Combo Therapy ($)
	80 mcg/ 200 mg 100 mcg/ 200 mg 120 mcg/ 200 mg 150 mcg/ 200 mg	2 pens/ 56 to 98 caps	786.3900 786.3900 868.9600 868.9600			9,437 to 20,855	9,437 to 20,855

HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir; M = millions; mcg = micrograms; mL= millilitre; mg = milligram; Peg-IFN = pegylated interferon; RBV = ribavirin.
[a] Manufacturer's confidential submitted price.
[b] 12 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.
[c] Ontario Drug Benefit Formulary (October 2014).
[d] Dosing varies by weight and HCV genotype.
[e] 12 weeks for genotype 1, 2, 4; 16 to 24 weeks for genotype 3.
[f] Sofosbuvir in combination with ribavirin (as a standalone drug) for 24 weeks can be considered as a therapeutic option for treatment-naive and non-cirrhotic treatment-experienced CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen.
[g] Quebec Provincial Drug Formulary (October 2014).
Source: Saskatchewan Drug Benefit (October 2014) prices unless otherwise stated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

All summary tables are based on the manufacturer's base-case results.

Subgroup: Genotype 1 (G1), treatment-naive (TN), intention-to-treat (ITT), 84% non-cirrhotic (60% eight weeks, 40% 12 weeks), 16% cirrhotic

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF+PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SIM = simeprevir.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$17,928 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year.

Subgroup: G1, TN, 100% non-cirrhotic (eight weeks)

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone	X					
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone	X					
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SIM = simeprevir.

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$17,953 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, TN, 100% non-cirrhotic (12 weeks)

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	$39,167 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 13: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SIM = simeprevir.

TABLE 14: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$29,330 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, TN, 100% cirrhotic (12 weeks)

TABLE 15: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir.

TABLE 16: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone		X				
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; SIM = simeprevir.

TABLE 17: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$5,772 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, treatment-experienced (TE), ITT, 80% non-cirrhotic, 20% cirrhotic

TABLE 18: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$21,696 per QALY $45,227 per life-year					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 19: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$10,141 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.

TABLE 20: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$27,545 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, TE, 100% non-cirrhotic

TABLE 21: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$3,686 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 22: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.

TABLE 23: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$29,834 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, TE, 100% cirrhotic

TABLE 24: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$53,421 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 25: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$28,104 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.

TABLE 26: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

Subgroup: G1, TE, protease inhibitor (PI) experienced

TABLE 27: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO NO TREATMENT?

LDV/SOF versus NT	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$27,274 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NT = no treatment; QALY = quality-adjusted life-year.

TABLE 28: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life						X
Incremental CE ratio or net benefit calculation	$24,557 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

Subgroup: G1, TN, ITT, 84% non-cirrhotic (12 weeks), 16% cirrhotic (network meta-analysis results)

TABLE 29: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SOF + PR?

LDV/SOF versus SOF + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	$23,334 per QALY					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 30: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LDV/SOF RELATIVE TO SIM + PR?

LDV/SOF versus SIM + PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)						X
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life						X
Incremental CE ratio or net benefit calculation	LDV/SOF dominates					

CE = cost-effectiveness; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.

The perspective was that of the government payer, as that was the perspective adopted by the manufacturer in its reported results.

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 31: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments (Reviewer to provide comments if checking "no")	None		
Was the material included (content) sufficient?		X	
Comments (Reviewer to provide comments if checking "poor")	None		
Was the submission well-organized and was information easy to locate?		X	
Comments (Reviewer to provide comments if checking "poor")			

TABLE 32: AUTHOR INFORMATION

Authors	Affiliations
	Athena Research Inc. OPTUM Insight UK

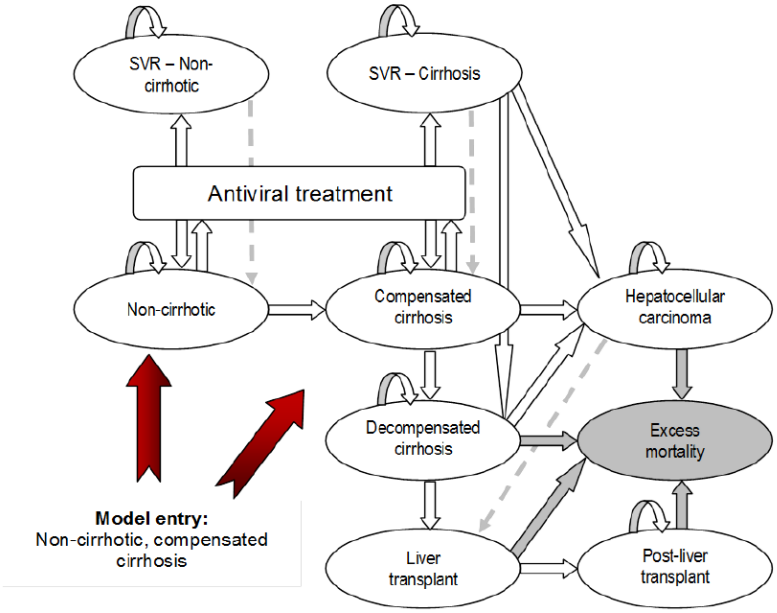
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The model structure is a simplification of the Shepherd et al. model, which had considerably more non-cirrhotic states. The natural history transition rates are based upon a number of different studies, including Grishchenko,[4] Fattovitch, Shepherd,[5] and Cardoso.[6] The effectiveness data are taken from the active groups of the pivotal trials for the six therapies being evaluated. Utility data (Health Utilities Index Mark 2 [HUI2] and Mark 3 [HUI3]) are taken from two relatively recent published surveys of a Canadian chronic hepatitis C (CHC) population, which appear to report companion studies, as they are from the same research team and use the same measures. Costs are based on expert accounts of the resource utilization, and the costs are taken from Ontario health care cost sources.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



** Patients can die in each health state. The gray health state title "excess mortality" represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma.*

SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[1]

TABLE 33: DATA SOURCES

Data Input	Description of Data Source	CDR Comment
Efficacy	The effectiveness estimates — SVR rates — were taken from the active intervention groups of pivotal trials. A sensitivity analysis used a Bayesian NMA to combine the data from the studies to provide an alternative measure of effect.	There is a high potential for bias in the estimates produced by observed SVR rates in the clinical trials. The PE report notes that disease stage has an impact upon the response to therapy. By extension, the authors must accept that variations in the case mix of the pivotal trial populations have the potential to introduce bias into the estimates of incremental effect.
Natural history	The CHC natural history parameters in the model are derived from a number of sources. Three studies are particularly important: Grishchenko et al. (2009); Fattovitch; and Shepherd.	The use of the Grishchenko et al. (2009) data to estimate a combined transition rate for non-cirrhotic to cirrhotic is problematic (see note below Manufacturer's Key Assumptions).
Utilities	The utility data were taken from Hsu et al. 2012, except for the value for the utility of sustained viral response. This was taken from a paper by John-Baptiste et al. The two papers are from the same research group, and used equivalent methods and measures.	The utilities used in the model have a number of problems. The HUI2 is designed for use with children. The valuation question explicitly asks the respondent to value health states from the perspective of a 10-year-old child with 50 years to live. Given the age of the cohort in the model is 45 years, and CHC is not a disease of childhood, it is hard to understand the choice of the HUI2. The choice is particularly difficult to understand as the studies reported data from the HUI3, SF6D, and direct TTO valuations from the same patients. A further concern is that while the HUI2 was used for the majority of the states, the utility increment for SVR (0.08) is from the HUI3, not the HUI2. However, these problems are relatively unimportant once we examine the regression models from which the utilities are derived. The parameters and statistical significance data for each model are provided. The majority of coefficients are not statistically significantly different from 0 (zero). As a result, none of the utilities from the Hsu et al. or John-Baptiste papers can be relied upon for use in the model. We therefore provide CDR results using alternative HUI utilities taken from Chong et al. (2003).[14]
Resource use	The resource use data are taken from Ontario Health System data sources, based upon expert clinical advice.	

Data Input	Description of Data Source	CDR Comment
Adverse effects (indicate which specific adverse effects were considered in the model)	The model considers three adverse effects: anemia, depression, and rash.	
Mortality	Age and gender-specific mortality rates were taken from Health Canada. Excess mortality data were applied to the cirrhotic, transplant, and hepatocellular cancer states. CHC-related mortality was taken from Fattovitch et al. (1997); transplant-related excess mortality was taken from Shepherd et al. (2007).	The excess mortality data are not Canadian. The CHC-specific excess mortality is from a European study (N = 384, five-year follow-up). The Shepherd Reference is another health technology assessment report and not a primary data source. Shepherd et al. use an even older study from 1993, reporting on a cohort of 176 patients followed up in Copenhagen between 1969 and 1987. The information provided in the report about the PSA is sparse; therefore, we cannot be confident that this uncertainty is adequately reflected in the submitted analyses.
Costs		
Drug	Ontario Drug Formulary	Where the dose is weight dependent, the assumed weight is 79 kg. 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.[11]	The majority (95.2%) of patients included in the Lachaine study were treated with PR only, which means that the 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 study by Dakin et al.[17]	These data are from a hepatitis B rather than hepatitis C patient population. This may have implications for the validity of the results, especially if the relative costs of treatment in different health states varies between hepatitis C and hepatitis B.

AE = adverse effect; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; HUI2 = Health Utilities Index Mark 2; HUI3 = Health Utilities Index Mark 3; NMA = network meta-analysis; PE = pharmacoeconomic; PSA = probabilistic sensitivity analysis; PR = pegylated interferon plus ribavirin; RAMQ = Régie de l'assurance maladie de Québec; SVR = sustained virologic response; TTO = time trade-off.

TABLE 34: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	CDR Comment
The non-cirrhotic stage combined the mild and moderate stages.	Inappropriate. While having equivalent quality of life weights, mild and moderate stages can have very different costs of care. This will increase the expected cost of care for early disease compared with a model that keeps the mild and moderate states separate. This artificially increases the expected value of eliminating the virus. Previous studies of the cost-effectiveness of treatments for CHC that have used mild and moderate CHC as separate disease states indicate a substantial difference in the costs of care.
Non-cirrhotic patients were classified as mild or moderate and the proportion was assigned as observed in SOF registration trials (77%:23%).	The use of the Grishchenko et al. (2009) data to estimate a combined transition rate for non-cirrhotic to cirrhotic is problematic (see note below).
25% of patients who experienced anemia would be managed with erythropoietin.	The study by Lachaine et al. reported that 17.7% of patients required erythropoietin.[11] This will overestimate the cost of anemia and favour LDV/SOF.

CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; LDV/SOF = ledipasvir/sofosbuvir; SOF = sofosbuvir.

Note: Problems with the natural history transition rate from non-cirrhotic to cirrhotic state
The manufacturers state that the transition rate for the non-cirrhotic to cirrhotic state is based upon Grishchenko et al. [4] In the Grishchenko paper, the non-cirrhotic state consists of mild and moderate CHC. Combining the transition rates for these two states into a single state should not lead to a constant transition rate, as the manufacturers report. To illustrate why this is the case, we will use the Grishchenko et al. transition rates for mild to moderate CHC and for moderate CHC to cirrhosis for the 40 years patient group. The mild to moderate annual transition rate is reported to be 0.023 (for genotype 1), and the moderate to cirrhotic transition rate is reported to be 0.032. [4]

If we start with a cohort of 10,000 patients — split 60/40 between the mild and moderate CHC states as in the original Grishchenko cohort — at the end of cycle 1, we would expect 3.2% of the moderate patients to transit to the cirrhotic state; and we would expect 2.3% of the mild patients to transit to the moderate state. If we group the two states into one state — non-cirrhotic — we would have 132.4 patients transit to the cirrhotic state from the non-cirrhotic state. The implied transition rate is 132.4 out of 10,000 = 1.32%.

In the second cycle, if we keep the states separate, we observe 135 patients go from mild to moderate, and 132 patients transit from moderate to cirrhotic, based upon the Grishchenko transition probabilities. The implied transition rate for the combined group is now 132 out of 9,868.

In each cycle, the denominator for the calculation of the transition rate changes and the rate of change depends upon the initial distribution of the cohort between the mild and moderate health states. The larger the proportion of the cohort starting in the moderate state, the closer the combined transition rate will be to the Grishchenko moderate-to-cirrhosis transition rate. The greater the proportion starting in the mild state, the further away from the Grishchenko moderate-to-cirrhosis transition rate the non-cirrhotic-to-cirrhotic transition rate will be and the greater the number of cycles it will take for the transition rate to reach the Grishchenko rate.

The CADTH Common Drug Review (CDR) could find no consideration of this issue in the manufacturer's submission, nor evidence as to whether the process for deriving the non-cirrhotic-to-cirrhotic transition rate used in the model had in some way incorporated this factor.

Manufacturer's Results

TABLE 35: BASE-CASE RESULTS, ALL PATIENT SUBGROUPS AND ALL COMPARATORS (TREATMENT-NAIVE)

Patient Subgroup	Treatment strategies	Δ SVR*	Δ Treatment Costs**	ICER ($/QALY)
G1 TN ITT	**LDV/SOF vs. SOF + P/R**	**6%**	[redacted]	LDV/SOF dominates
84% non-cirrhotic	LDV/SOF vs. SIM + P/R	17%		LDV/SOF dominates
- 60% 8 week	LDV/SOF vs. TPV + P/R	22%		LDV/SOF dominates
- 40% 12 week	LDV/SOF vs. BOC + P/R	34%		LDV/SOF dominates
16% cirrhotic	LDV/SOF vs. SOF +RBV	33%		LDV/SOF dominates
	LDV/SOF vs. NT	95%		17,928 $/QALY
G1 TN	LDV/SOF vs. SOF + P/R	3%		LDV/SOF dominates
non-cirrhotic	LDV/SOF vs. SIM + P/R	12%		LDV/SOF dominates
subgroup	LDV/SOF vs. TPV + P/R	19%		LDV/SOF dominates
- 8 weeks	LDV/SOF vs. BOC + P/R	28%		LDV/SOF dominates
	LDV/SOF vs. SOF +RBV	26%		LDV/SOF dominates
	LDV/SOF vs. NT	94%		17,953 $/QALY
G1 TN	LDV/SOF vs. SOF + P/R	5%		39,167 $/QALY
non-cirrhotic	LDV/SOF vs. SIM + P/R	15%		LDV/SOF dominates
subgroup	LDV/SOF vs. TPV + P/R	21%		12,389 $/QALY
- 12 weeks	LDV/SOF vs. BOC + P/R	31%		12,926 $/QALY
	LDV/SOF vs. SOF +RBV	29%		LDV/SOF dominates
	LDV/SOF vs. NT	97%		29,330 $/QALY
G1 TN	LDV/SOF vs. SOF + P/R	16%		LDV/SOF dominates
100% cirrhotic	LDV/SOF vs. SIM + P/R	37%		LDV/SOF dominates
subgroup	LDV/SOF vs. TPV + P/R	35%		LDV/SOF dominates
- 12 weeks	LDV/SOF vs. BOC + P/R	55%		LDV/SOF dominates
	LDV/SOF vs. SOF +RBV	61%		LDV/SOF dominates
	LDV/SOF vs. NT	97%		5,772 $/QALY

BOC + PR = boceprevir plus pegylated interferon plus ribavirin; G1 = genotype 1; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; LDV/SOF = ledipasvir/sofosbuvir; NT = no treatment; QALY = quality-adjusted life-year; SOF + RVB = sofosbuvir plus ribavirin; SVR = sustained virologic response; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin; TE = treatment-experienced; TN = treatment-naive; TEL + PR = telaprevir plus pegylated interferon plus ribavirin.
Source: Manufacturer's pharmacoeconomic submission, p.32.[1]

TABLE 36: BASE-CASE RESULTS, ALL PATIENT SUBGROUPS AND ALL COMPARATORS (TREATMENT-EXPERIENCED)

Patient Subgroup	Treatment strategies	Δ SVR*	Δ Treatment Costs**	ICER ($/QALY)
G1 TE 80% non-cirrhotic 20% cirrhotic	**LDV/SOF vs. SOF + P/R**	**25%**	[redacted]	**21,696 $/QALY**
	LDV/SOF vs. SIM + P/R	31%		10,141 $/QALY
	LDV/SOF vs. TPV + P/R	29%		15,717 $/QALY
	LDV/SOF vs. BOC + P/R	38%		5,077 $/QALY
	LDV/SOF vs. SOF + RBV	35%		LDV/SOF dominates
	LDV/SOF vs. NT	96%		27,545 $/QALY
G1 TE non-cirrhotic subgroup	LDV/SOF vs. SOF + P/R	24%		3,686 $/QALY
	LDV/SOF vs. SIM + P/R	27%		LDV/SOF dominates
	LDV/SOF vs. TPV + P/R	23%		6,503$/QALY
	LDV/SOF vs. BOC + P/R	31%		LDV/SOF dominates
	LDV/SOF vs. SOF + RBV	28%		LDV/SOF dominates
	LDV/SOF vs. NT	95%		29,834 $/QALY
G1 TE cirrhotic subgroup	LDV/SOF vs. SOF + P/R	29%		53,421 $/QALY
	LDV/SOF vs. SIM + P/R	46%		28,104 $/QALY
	LDV/SOF vs. TPV + P/R	53%		24,967 $/QALY
	LDV/SOF vs. BOC + P/R	65%		15,915 $/QALY
	LDV/SOF vs. SOF + RBV	64%		LDV/SOF dominates
	LDV/SOF vs. NT	100%		LDV/SOF dominates
G1 TE (PI-experienced)	**LDV/SOF vs. NT**	**97%**		**27,274 $/QALY**
	LDV/SOF vs. SOF + P/R	23%		24,557 $/QALY

*(LDV/SOF SVR) – (comparator SVR); ** (DLV/SOF treatment costs) – (comparator treatment costs)

BOC + PR = boceprevir plus pegylated interferon plus ribavirin; G1 = genotype 1; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; LDV/SOF = ledipasvir/sofosbuvir; NT = no treatment; PI = protease inhibitor; QALY = quality-adjusted life-year; SOF + RVB = sofosbuvir plus ribavirin; SVR = sustained virologic response; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin; TE = treatment-experienced; TN = treatment-naive; TEL + PR = telaprevir plus pegylated interferon plus ribavirin.
Source: Manufacturer's pharmacoeconomic submission, p.34.[1]

CADTH Common Drug Review Reanalysis

CDR performed a number of reanalyses in which CDR reviewers corrected mistakes regarding the calculation of incremental cost-utility ratios (ICURs) by using the outputs of the probabilistic sensitivity analysis (PSA). CDR also increased the number of simulations to 20,000 to provide confidence that the means and standard errors of the output distributions were stable.

The following reanalyses were performed:

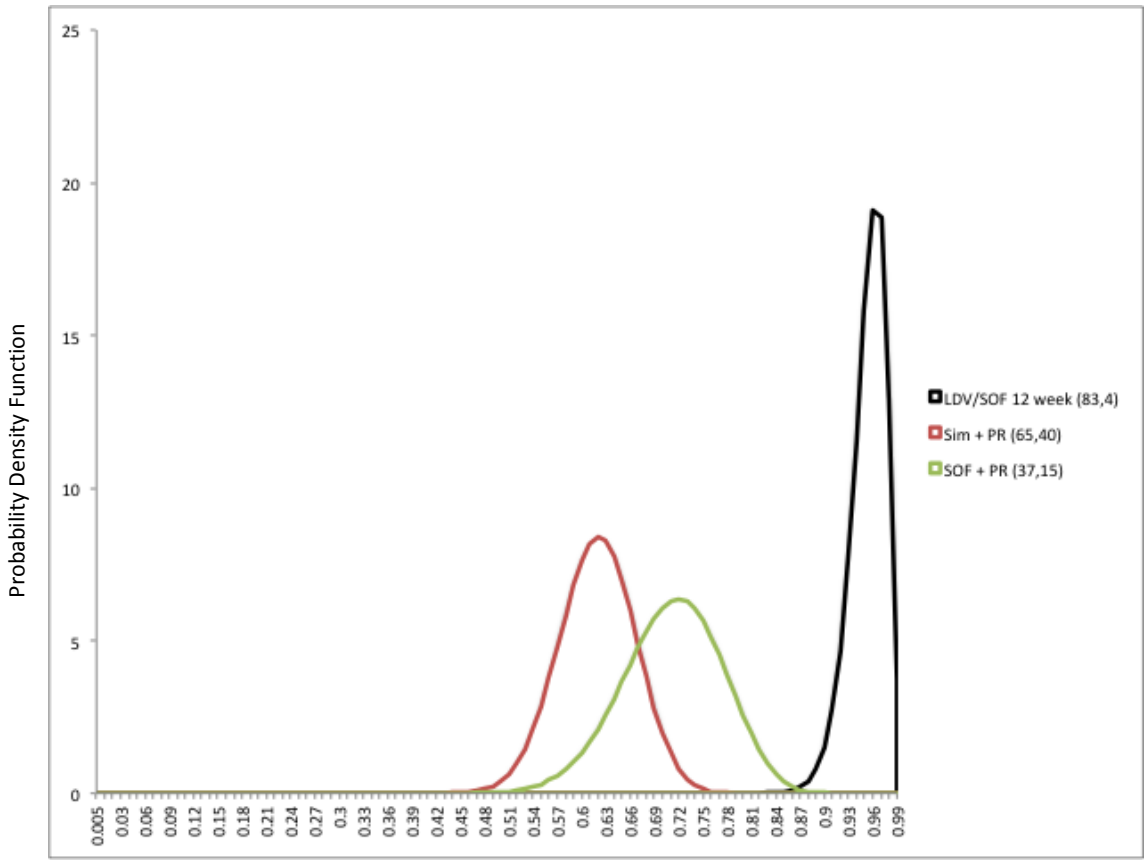
- Exploration of the uncertainty with sustained virologic response (SVR) rates in treatment-experienced (TE) cirrhotic patients due to the small sample size in the ION-2 trial
- Alternative utility values (HUI3 from Chong 2003[14])
- Reduced cost of anemia: CDR will assign a cost of anemia that is 12.5% of the RAMQ cost (0.125 × $10,787 = $1,348.38) instead of the $2,696.85 used by the manufacturer
- Proportion of patients eligible for short duration of pegylated interferon(Peg-IFN) based on response-guided therapy (RGT) in the simeprevir plus PR (SIM + PR) group: the manufacturer assumed 41% and 52% of patients would receive PR for 24 and 48 weeks, respectively, which results

in an average duration (used to calculate costs of PR) of 36 weeks. To account for the treatment-naive and prior-relapse patients eligible for 24 weeks of PR (ranging from 79% to 93% of patients), CDR will assume a revised duration of PR of 26 weeks instead of 36 weeks.

Exploratory analysis of the uncertainty in comparative SVR rates

Figure 2 shows the beta distributions of the SVR rates in the non-cirrhotic TE patients who received 12 weeks therapy. As shown on the figure, there is little overlap between LDV/SOF and comparators.

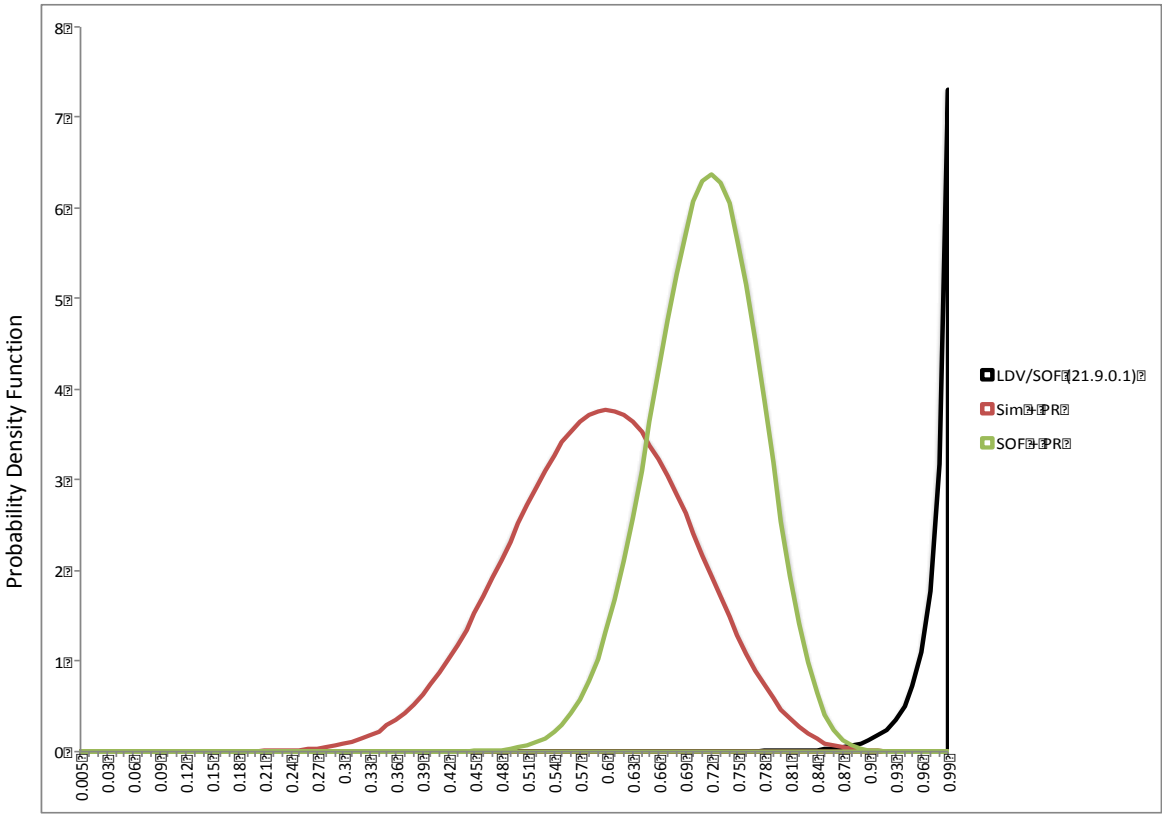
FIGURE 2: BETA DISTRIBUTIONS OF THE SUSTAINED VIROLOGIC RESPONSE RATES IN NON-CIRRHOTIC TREATMENT-EXPERIENCED PATIENTS



LDV/SOF = ledipasvir/sofosbuvir; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

Figure 3 shows the beta distributions of the SVR rates in the non-cirrhotic TE patients who received 12 weeks therapy. As shown in the figure, there is little overlap between LDV/SOF and comparators.

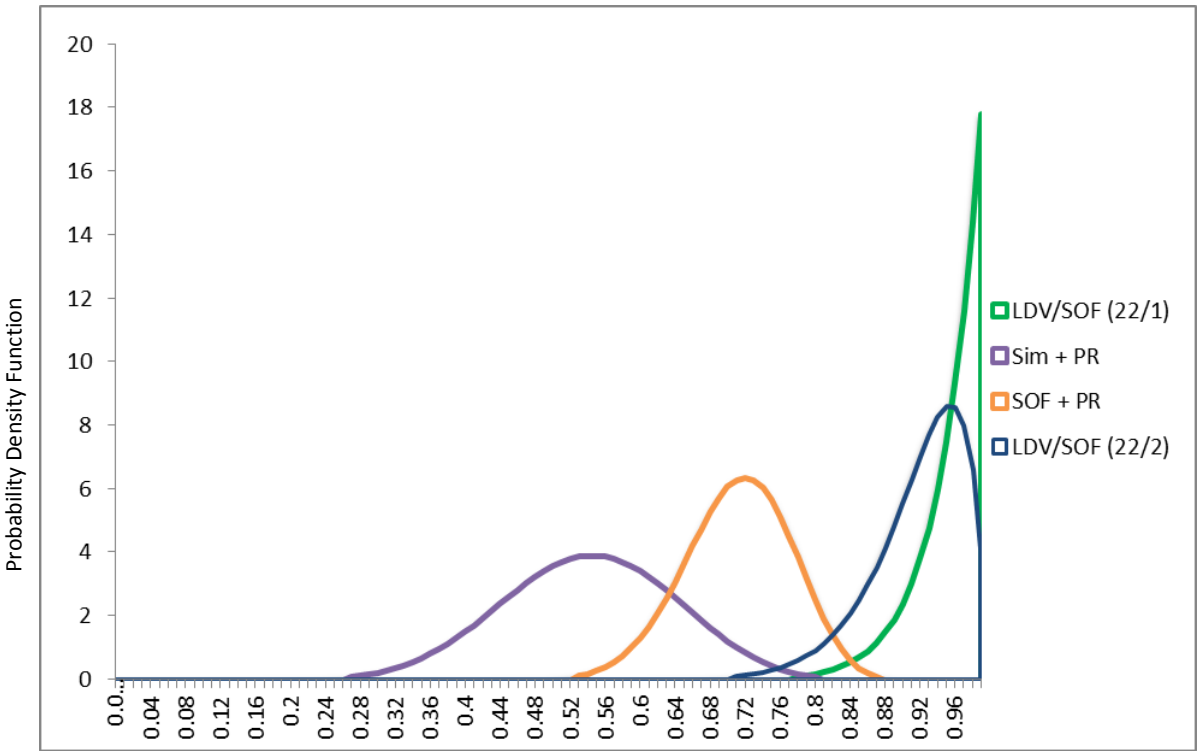
FIGURE 3: BETA DISTRIBUTIONS FOR TREATMENT-EXPERIENCED CIRRHOTIC PATIENTS' SUSTAINED VIROLOGIC RESPONSE RATES IN EXPLORATORY ANALYSIS



LDV/SOF = ledipasvir/sofosbuvir; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

CDR plotted two alternative beta distributions for LDV/SOF. The first assumes that a hypothetical 23rd patient was a non-responder (green plot: LDV/SOF 22/1); the second assumes that two additional patients did not respond (blue plot: LDV/SOF 22/2). It is clear that two additional data points could radically change the relative advantage of LDV/SOF compared with alternative therapies (there would be more overlap between LDV/SOF and SOF + PR, SIM + PR).

FIGURE 4: ILLUSTRATION OF THE SENSITIVITY OF LDV/SOF SUSTAINED VIROLOGIC RESPONSE TO ONE (LDV/SOF 22/1) AND TWO (LDV/SOV 22/2) ADDITIONAL DATA POINTS



LDV/SOF = ledipasvir/sofosbuvir; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

Alternative utility values

Table 35 presents the results of CDR reanalyses using utility values from Chong et al. LDV/SOF remained cost-effective in TE non-cirrhotics and prior protease inhibitor failure, but the ICUR for LDV/SOF compared with SOF + PR in TE cirrhotics was $59,715 per QALY, and the PSA showed a 28% probability that the ICUR would be < 50,000 per QALY.

TABLE 37: CDR REANALYSIS USING ALTERNATE UTILITY VALUES

	Absolute		Incremental Analysis			
	Costs	**QALYs**	**Costs**	**QALYs**	**ICUR**	**% ICUR < $50K per QALY**
Genotype 1, Treatment-Experienced Non-Cirrhotic						
LDV/SOF (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	$5,531	100%
SOF + PR (12 weeks)	[redacted]	[redacted]	Baseline treatment			
SIM + PR	$57,490	12.15	Dominated			
Genotype 1, Treatment-Experienced Cirrhotic						
LDV/SOF (24 weeks)	$139,874	11.31	$47,175	0.79	$59,715	28%
SOF + PR (12 weeks)	$92,699	10.52	Baseline treatment			
SIM + PR	$102,059	9.99	Dominated by SOF + PR			
Genotype 1, Treatment PI + PR Failures						
LDV/SOF (12 weeks/24 weeks cirrhotics)	[redacted]	[redacted]	[redacted]	[redacted]	$40,514	83%
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
No treatment	$23,661	11.02	Baseline treatment			

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

Reduced cost of anemia

Table 38 presents the results of CDR reanalyses using a lower cost of anemia ($1,348.38 instead of $2,696.85).

TABLE 38: CDR REANALYSIS USING LOWER COST OF ANEMIA

	Absolute		Incremental Analysis			
	Costs	**QALYs**	**Costs**	**QALYs**	**ICUR**	**% ICUR < $50K per QALY**
Genotype 1, Treatment-Experienced Non-Cirrhotic						
LDV/SOF (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	$6,503	100%
SOF + PR (12 weeks)	[redacted]	[redacted]	Baseline treatment			
SIM + PR	$57,505	12.15	Dominated			
Genotype 1, Treatment-Experienced Cirrhotic						
LDV/SOF (24 weeks)	$139,904	11.31	$47,545	0.79	$60,273	27%
SOF + PR (12 weeks)	$92,359	10.52	Baseline treatment			
SIM + PR	$102,077	10.08	Dominated by SOF + PR			
Genotype 1, Treatment PI + PR Failures						
LDV/SOF (12 weeks/24 weeks cirrhotics)	[redacted]	[redacted]	[redacted]	[redacted]	$40,630	NA
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
No treatment	$23,673	11.01	Baseline treatment			

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-years; SIM + PR = simeprevir + pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

LDV/SOF remained cost-effective in TE non-cirrhotics and prior PI failure, but the ICUR for LDV/SOF compared with SOF + PR in TE cirrhotics was $60,273 per QALY, and the PSA showed a 27% probability that the ICUR would be < $50,000 per QALY.

Duration of PR in the SIM + PR group

TABLE 39: CDR REANALYSIS USING 26 WEEKS OF PEGYLATED INTERFERON PLUS RIBAVIRIN IN THE SIM + PR GROUP

	Absolute		Incremental Analysis			
	Costs	**QALYs**	**Costs**	**QALYs**	**ICUR**	**% ICUR < $50K per QALY**
Genotype 1, Treatment-Experienced Non-Cirrhotic						
LDV/SOF (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	$15,100	100%
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
SIM + PR	$50,977	12.16	Baseline treatment			
Genotype 1, Treatment-Experienced Cirrhotic						
LDV/SOF (24 weeks)	$139,858	11.31	$47,069	0.79	$59,916	29%
SOF + PR (12 weeks)	$92,788	10.52	Baseline treatment			
SIM + PR	$95,591	10.06	Dominated by SOF + PR			
Genotype 1, Treatment PI + PR Failures						
LDV/SOF (12 weeks/24 weeks cirrhotics)	[redacted]	[redacted]	[redacted]	[redacted]	$40,786	NA
SOF + PR (12 weeks)	[redacted]	[redacted]	Extendedly dominated			
No treatment	$23,661	11.02	Baseline treatment			

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SIM + PR = simeprevir plus pegylated interferon plus ribavirin; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

LDV/SOF remained cost-effective in the TE non-cirrhotic and prior PI failure groups, but the ICUR for LDV/SOF compared with SOF + PR in TE cirrhotics was $59,916 per QALY, and the PSA showed a 29% probability that the ICUR would be < $50,000 per QALY.

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