Common Drug Review
Pharmacoeconomic Review Report

June 2015

Drug	ombitasvir, paritaprevir, ritonavir and dasabuvir (OBV/PTV/RTV and DSV)
Indication	For the treatment of adults with genotype 1 chronic hepatitis C virus infection, including those with compensated cirrhosis.
Listing request	For the treatment of genotype 1 chronic hepatitis C infection, including patients who are treatment-naive or who have failed previous therapies against hepatitis C virus and patients with compensated cirrhosis.
Manufacturer	AbbVie Corporation

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

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

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

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ABBREVIATIONS

AE	adverse event
BOC	boceprevir
CHC	chronic hepatitis C infection
DSV	dasabuvir
EMEA	European Medicines Agency
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
LDV/SOF	ledipasvir/sofosbuvir
OBV/PTV/RTV	ombitasvir/paritaprevir/ritonavir
PR	pegylated interferon and ribavirin
QALY	quality-adjusted life-years
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
TEL	telaprevir

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	OBV/PTV/RTV and DSV with or without RBV					
Study Question	What is the cost-effectiveness of OBV/PTV/RTV and DSV ± RBV in the treatment of naive or experienced patients with genotype 1a or b chronic hepatitis C in Canada					
Type of Economic Evaluation	CUA					
Target Population	Patients with chronic hepatitis C viral infection genotype 1 in the following subgroups: (1) treatment-naive and (2) treatment-experienced with PR, which is further categorized by: null responders, partial responders, and prior relapses.					
Treatment	OBV/PTV/RTV and DSV oral for 8 weeks, 12 weeks, or 24 weeks					
Outcomes	SVR and QALYs					
Comparator(s)	LDV/SOF, SOF + PR, TEL + PR, BOC + PR, and SIM + PR					
Perspective	Government					
Time Horizon	Lifetime horizon (70 years)					
Results for Base Case	**Indication**	**ICUR OBV/PTV/ RTV and DSV vs. LDV/SOF ($/QALY)**	**ICUR OBV/PTV/ RTV and DSV vs. SOF + PR ($/QALY)**	**ICUR OBV/PTV/ RTV and DSV vs. SIM + PR ($/QALY)**	**ICUR OBV/PTV/ RTV and DSV vs. BOC + PR ($/QALY)**	**ICUR OBV/PTV/ RTV and DSV vs. TEL + PR ($/QALY)**
	Treatment-naive	Dominant	Dominant	$17,003	$26,699	$19,196
	Null responder	Less costly, fewer QALY gains	TBD	TBD	TBD	$6,600
	Partial responder	Dominant	TBD	TBD	Dominant	Dominant
	Prior relapser	Less costly, fewer QALY gains	TBD	$18,086	$1,773	$16,011
	Treatment-experienced (overall)	Less costly, fewer QALY gains	TBD	TBD	TBD	$6,268
	Source: Adapted from the manufacturer's pharmacoeconomic submission.					
Key Limitations	CDR identified a number of limitations with the manufacturer's submission: 1. Effectiveness estimates were from separate non-comparative and potentially non-comparable trials. 2. The natural history model is based on publications from 1997 and relatively small studies, while more recent and robust sources were available. 3. Treatment-related utility decrement with SOF + PR is likely overestimated. 4. The cost of anemia was likely overestimated, which favours OBV/PTV/RTV and DSV due to its lower incidence of anemia. 5. The utility data collected in the trial program were not used in the base-case analysis. Inputs were obtained from older studies of lower quality. 6. Comparative reinfection rate in patients treated with interferon-free regimens versus those treated with PR-based therapies is unknown and was not properly explored. CDR was unable to account for all the above limitations in reanalyses. CDR reanalyses using different treatment-related utility decrement and lower anemia cost showed no significant differences from the manufacturer's results, but there remains considerable uncertainty regarding the comparative cost-effectiveness of OBV/PTV/RTV and DSV compared with other treatment regimens.					

[redacted]	The comparative cost-effectiveness of OBV/PTV/RTV and DSV and LDV/SOF is unstable and sensitive to variations in drug price. The evidence provided in the manufacturer's submission does not provide robust evidence of the likely cost per QALY in all the varied patient groups that are likely to seek treatment with interferon-free regimens from Canadian health care systems.

BOC = boceprevir; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained viral response; TBD = to be determined because cannot be assessed with current available data; TEL = telaprevir.

EXECUTIVE SUMMARY

Background

Ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) fixed-dose combination and dasabuvir (DSV) (Holkira Pak) is an all-oral interferon-free regimen indicated for the treatment of adults with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. The recommended dose of OBV/PTV/RTV and DSV is two OBV 12.5 mg/PTV 75 mg/RTV 50 mg tablets once daily and one DSV 250 mg tablet twice daily for 12 weeks (24 weeks for patients with HCV genotype 1a infection with cirrhosis who have had a previous null response to pegylated interferon and ribavirin [PR]).[1] The manufacturer submitted a confidential price of $[redacted] per daily blister pack (containing two tablets of OBV/PTV/RTV and two tablets of DSV), corresponding to $[redacted] for a 12-week treatment and $[redacted] for a 24-week treatment.[2]

OBV/PTV/RTV and DSV is used in combination with ribavirin in patients with HCV genotype 1a infection and all patients with HCV who have cirrhosis. It can be used without ribavirin in patients with genotype 1b infection without cirrhosis. In January 2015, a stand-alone ribavirin 200 mg tablet (Moderiba) commercialized by AbbVie received a Notice of Compliance.[3] The daily dose of Moderiba in combination with OBV/PTV/RTV and DSV is 1,000 mg for patients who weigh less than 75 kg, and 1,200 mg for patients who weigh 75 kg or more, administered orally in two divided doses.[3] In the pharmacoeconomic report, the manufacturer states that Moderiba will be provided by AbbVie Canada Inc. free of charge in combination with OBV/PTV/RTV and DSV when required.[4]

The manufacturer submitted a cost-utility analysis (CUA) conducted over a patient's lifetime (70 years) from a government payer perspective. The manufacturer's base-case analyses compared OBV/PTV/RTV and DSV with five comparators: ledipasvir/sofosbuvir (LDV/SOF), sofosbuvir plus PR (SOF + PR), telaprevir plus PR (TEL + PR), boceprevir plus PR (BOC + PR), and simeprevir plus PR (SIM + PR). The model structure is based upon the original Hepatitis C Cost-Effectiveness Model published by Bennett (1997)[5] and consists of 10 distinct health states. In the base-case analysis, the manufacturer examined the cost-effectiveness of OBV/PTV/RTV and DSV in a treatment-naive cohort (composed of 62.6%, 24.4%, and 11% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; 66.4% with genotype 1a), and a treatment-experienced cohort (composed of 47.3%, 23.3%, and 29.4% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; and 66.4% with genotype 1a). The manufacturer reported that OBV/PTV/RTV and DSV is either dominant, highly cost-effective, or substantially less expensive than alternatives with slightly fewer quality-adjusted life-year (QALY) gains.

Summary of Identified Limitations and Key Results

While the submission from the manufacturer adopts a similar approach to a number of other models of the cost-effectiveness of treatments for HCV, it does not make use of the best available evidence and this affects the confidence that can be placed on the submitted results, and limits the CADTH Common Drug Review's (CDR's) ability to provide additional and more robust analyses. The following limitations were of particular concern: effectiveness estimates were from separate non-comparative and likely non-comparable trials and failure to compare active treatments with "no treatment" in the base case. Given the large number of HCV patients who do not currently seek active treatment, this is a relevant comparator that should have been included in the analysis.

Further, the evidence used for the manufacturer's natural history model is based on a publication from 1997 and relatively small studies. A more recent study by Thein (2008)[6] provides nuanced insight into the cost-effectiveness of OBV/PTV/RTV and DSV, given the assessment of progression data for different populations. Finally, the utility data used for the base-case analysis were not those collected in the clinical trial program but rather from older publications that appear to reflect lower-quality studies.

Conclusions

A number of limitations were identified with the manufacturer's economic submission. The model structure and many of the parameters were not drawn from the best available evidence; however, these issues likely affect comparators and OBV/PTV/RTV and DSV equally. That said, the estimates of absolute costs and QALYs should be viewed with caution. This is important if decision-makers are interested in the cost-effectiveness of interferon-free chronic hepatitis C therapies compared with no active treatment, a treatment option that may be chosen by patients in preference to interferon-comparing regimens. For this comparison, the absolute benefit of the interferon-free regimens will drive the expected cost-effectiveness.

The evidence submitted suggests that OBV/PTV/RTV and DSV leads to similar QALYs compared with LDV/SOF. The incremental cost-utility ratio (ICUR) of OBV/PTV/RTV and DSV versus LDV/SOF was sensitive to variations in drug price. As well, OBV/PTV/RTV and DSV is likely to lead to ICURs within commonly accepted thresholds versus other comparators in those patients who would currently receive PR therapy, although ICURs were sensitive to variations in drug prices and were based on naive indirect comparison of efficacy and safety. As such, there is significant uncertainty regarding the comparative cost-effectiveness of OBV/PTV/RTV and DSV compared with other treatment regimens.

The submitted analyses do not provide insight into the likely cost-effectiveness of OBV/PTV/RTV and DSV in other patient groups such as community-dwelling patients (patients screened for HCV in a non-clinical setting) or patients who would currently be managed with watchful waiting.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer has submitted cost-utility analyses (CUAs) based upon a Markov model that consists of 10 distinct health states.[4] The model structure is based upon the original Hepatitis C Cost-Effectiveness Model published by Bennett et al. (1997).[5] Four states focus on pre-cirrhotic disease with and without hepatitis C ("mild fibrosis" and "moderate fibrosis"). There are two compensated cirrhosis states — again, with and without hepatitis C; more severe disease is separated into "decompensated cirrhosis," "hepatocellular carcinoma" (HCC), and "liver transplant." The final model state is "dead." In contrast to some recent cost-effectiveness analysis models, the submitted analysis allows for reinfection (but assumes no re-treatment upon reinfection). Decompensated cirrhosis, HCC, and liver transplant have a liver-specific risk of death as well as the all-cause mortality that applies to all other health states. The model structure is a simplification of the original model, which had highly disaggregated advanced liver diseases states: nine in total compared with the four states in this model (Figure 1 in Appendix 4).

The model is used to estimate the impact of sustained virologic response (SVR) — the interim outcome used in the trials and the primary outcome of interest on long-term health gain measured using quality-adjusted life-years (QALYs). The natural history model parameters (transition matrix) are derived from the large scale meta-analysis of chronic hepatitis C (CHC) epidemiology studies reported by Thein et al.[6] and other sources. The authors report that they used the Excel Solver function to convert the results from Thein et al. to transition probabilities for mild fibrosis to moderate fibrosis and moderate fibrosis to cirrhosis. They validate their aggregated transition data against Thein's estimate of the proportion of patients who would reach compensated cirrhosis at 20 years.

The patient cohort is assumed to have a mean age of 52 at the start of the model, and is followed up over a lifetime (up to 70 years' duration). The cohort consists of a mixture of cirrhotic and non-cirrhotic patients, and separate analyses are undertaken for treatment-naive (composed of 62.6%, 24.4%, and 11% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; and 66.4% with genotype 1a) and treatment-experienced (composed of 47.3%, 23.3%, and 29.4% of patients with mild fibrosis, moderate fibrosis, and compensated cirrhosis, respectively; and 66.4% with genotype 1a) cohorts. The treatment-experienced cohort is further stratified by type of prior response: null responders, partial responders, and prior relapses.

The manufacturer provides analyses comparing ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) and dasabuvir (DSV) to five comparators: ledipasvir/sofosbuvir (LDV/SOF), sofosbuvir plus pegylated interferon and ribavirin (SOF + PR), simeprevir plus PR (SIM + PR), boceprevir plus PR (BOC + PR), and telaprevir plus PR (TEL + PR). Notably, the manufacturers did not include a watchful waiting or no-treatment comparator, even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimes. The effectiveness data and incidence of specific adverse events (AEs) (anemia, rash, depression, neutropenia, and thrombocytopenia) are taken from the active groups of the pivotal trials for the five therapies being evaluated (naive indirect comparison).

Utility data for mild fibrosis, moderate fibrosis, and compensated cirrhosis are taken from a previous CADTH report (Brady et al. 2007).[7] These are Health Utilities Index Mark 3 (HUI3) utilities from a 2003

study by Chong et al.[8] In Brady et al., all of the four milder health states are given the same utility score (0.73). Decompensated cirrhosis incurs a decrement of 0.04, and the utility for HCC is 0.51. Liver transplant is assumed to improve health-related quality of life to 0.7. The long-term utility increment for being virus free is 0.04, while the utility decrement associated with treatment varies by treatment and is based on several sources.

Costs are taken from a wide range of studies. Updated figures from Brady et al. (CADTH 2007)[7] are used for mild fibrosis, moderate fibrosis, and compensated cirrhosis; patients who achieve SVR are assumed to incur 50% of these costs. The cost for decompensated cirrhosis is ascribed to a study by Krahn et al. (2005),[9] but this in turn was taken from a US study by Kim et al. (1997).[10] Costs indicated in the Brady et al. study are reportedly derived from literature review, clinical management literature, and expert physician opinion, with unit costs provided by Alberta sources. Cost of ribavirin is assumed to be $0. Cost of AEs are taken from a study by Lachaine et al. (2014).[11,12]

2. MANUFACTURER'S BASE CASE

In the analyses presented by the manufacturer, OBV/PTV/RTV and DSV is either dominant, highly cost-effective, or substantially less expensive than an alternative that is slightly more effective (Table 25 in Appendix 4).

Unfortunately, in treatment-experienced patient groups, the cost-effectiveness of SOF + PR and SIM + PR is unknown. The manufacturer also provides only partial results for treatment-experienced patient subgroups for BOC + PR.

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer's submission includes a range of single and multi-way deterministic sensitivity analyses. Health state and treatment utilities were varied between upper and lower bounds; health state costs were also varied between upper and lower bounds. Multi-way deterministic sensitivity analysis considered varying SVR rates, health state costs, and utilities. Scenario analyses examined differences in discount rate and differences arising from varying the distribution of the patient population between genotype 1a (G1a) and genotype 1b (G1b).

Probabilistic sensitivity analysis (PSA) was undertaken with appropriate distributions applied correctly to all parameters included in the PSA, based on 500 iterations. The manufacturer concludes that, on the cost-effectiveness acceptability frontier (CEAF), OBV/PTV/RTV and DSV is the optimal therapy if a public payer is willing to pay $30,000 per QALY in genotype 1 treatment-naive patients. OBV/PTV/RTV and DSV is also the optimal therapy in the treatment-experienced segments in the CEAF, as long as payers are willing to pay $19,000 per QALY.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

There are a number of important limitations with the manufacturer's economic submission, which limit the confidence that can be placed on the submitted estimates of cost-effectiveness.

3.1 The Effectiveness Parameters Used in the Model are Drawn From Non-comparative Trials

The manufacturer notes that an attempt was made to compare efficacy and safety of OBV/PTV/RTV and DSV with comparators using a network meta-analysis approach. Due to limitations caused by the lack of appropriate data and to avoid introducing additional uncertainty in the model, the manufacturer determined that the most transparent approach would be to use the unadjusted values from published trials.[4] Several assumptions and imputations were needed to obtain SVR rates in some subgroups. It is not possible for the CADTH Common Drug Review (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 capture the magnitude of the incremental benefit of OBV/PTV/RTV and DSV.

3.2 Natural History Data

The data source for the natural history seems to have been chosen to achieve coherence with the model structure used by Brady et al. (2007),[7] even though a more recently published, robust study is available by Thein et al. (2008).[6] The Thein et al. paper is more disaggregated in terms of the fibrosis stages; however, this should have no impact on the feasibility of modelling the effectiveness of therapy as SVR — unless there was reason to believe that the likelihood of SVR varied substantially between the METAVIR stages. Using the Thein et al. structure would also have enabled the submission to examine variations in the cost-effectiveness of the therapies according to the type of population being treated. The manufacturer's submission acknowledges that the rate of disease progression varies substantially between clinic and community HCV patient populations. The Brady et al. data speak to clinic-based populations rather than community-based populations. With only 6% of patients in community-based populations expected to be cirrhotic after 20 years, compared with 16% of clinic-based populations, the value proposition of OBV/PTV/RTV and DSV (and other oral antiviral therapies) will be substantially different. Thein et al. (2008)[6] report a substantial variation in transition rates across patient subgroups. The manufacturer's exclusion of the Thein natural history data is a notable concern.

The combination of the natural history and the health state utility data not considered by the manufacturer limits the confidence that can be placed on the results of the model, either for OBV/PTV/RTV and DSV or any of the other oral comparators reported.

3.3 Treatment-Related Utility Decrement With SOF + PR is Likely Overestimated

The manufacturer estimates the utility decrement for SOF + PR regimen from a poster by Younossi et al.[13] The figure (0.145) is taken from the maximum utility decrement observed in the Neutrino study at 12 weeks, not the mean utility decrement. There is no evidence to justify why patients on SOF + PR would experience a greater utility decrement during treatment (0.145) compared with patients receiving SIM + PR (0.081).

3.4 The Cost of Anemia was Likely Overestimated

The cost of anemia used by the manufacturer from the study by Lachaine et al. ($8,304 per patient) is driven by the cost of erythropoietin (estimated at $8,281 per patient, while the costs of medical visits and procedures are estimated at $23 per patient).[12] This is an overestimation, as reducing the dose of ribavirin is often sufficient to control anemia; thus, no erythropoietin would be needed. Of note, in another study by Lachaine et al.,[14] it was reported that only 17.7% of patients with anemia required erythropoietin. The overestimation of the cost of anemia will favour OBV/PTV/RTV and DSV (and LDV/SOF) compared with PR-containing regimens.

3.5 The Health State Utility Data Used in the Base-Case Analysis are From a Small 2003 Study; More Recent and Valid Sources Could Have Been Used

The majority of the utilities used in the manufacturer's base case are based upon data from fewer than 40 patients. This weakness in the choice of utility values was avoidable as the OBV/PTV/RTV and DSV phase 3 trials collected quality of life data from more than 2,000 patients. A further advantage of using this data would have been that the uncertainty in the majority of the model's utility parameters would have been much reduced, which would have reduced the uncertainty regarding the therapies' cost-effectiveness. Of note, in one sensitivity analysis, the manufacturer assumed that the chronic HCV (mild, moderate, and compensated cirrhosis) states were based on Holkira Pak baseline trial EuroQol 5-Dimensions Questionnaire (EQ-5D) observations. Few details were provided regarding which specific trials were included (treatment-naive and/or treatment-experienced patients).

3.6 Probability of Reinfection and its Impact on the Cost-Effectiveness of Holkira Pak and Other Interferon-Free Regimens is Uncertain

The inclusion of reinfection in the manufacturer's model is an important component, and as such is a strength of the approach adopted by the manufacturer. The manufacturer arbitrarily set the probability of reinfection at 1% per year and used this figure for its analyses. It would have been useful to examine what level of reinfection would lead to OBV/PTV/RTV and DSV ceasing to be cost-effective compared with alternative active therapies, and indeed compared with watchful waiting. In addition, it is likely that the risk of reinfection varies substantially by population subgroups (e.g., between drug users and blood donors), providing another reason why consideration should have been given to using the Thein et al. (2008) data to structure and parameterize the natural history model. CDR performed a threshold analysis to assess what rate of reinfection would result in OBV/PTV/RTV and DSV no longer dominating SOF + PR (see Issues for Consideration, and Table 40 in Appendix 4).

4. CADTH COMMON DRUG REVIEW ANALYSES

Many of the concerns detailed above cannot be addressed through simple correction of 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 to demonstrate the impact of correcting the anemia cost and the utility decrement for PR treatment regimens. CDR also provided ICURs based upon the probabilistic analysis, with 10,000 runs. CDR focused on the comparison of OBV/PTV/RTV and DSV with LDV/SOF and SOF + PR, as these were the two regimens that provided highest QALY gains.

- **Treatment-related disutility with SOF + PR:** There is no evidence to justify why patients on SOF + PR would experience a 12-week decrement (0.145) greater than the 24-week decrement assumed for patients receiving SIM + PR (0.081). Of note, Stepanova et al.[15] demonstrated that it is the interferon component of the SOF + PR regimen that has the greatest impact on quality of life.
  Therefore, CDR applied a 12-week utility decrement for SOF + PR of 0.081 (equivalent to the 24-week utility decrement assumed for SIM + PR). When annualized, this led to 0.081 x (12/52)= 0.019 instead of 0.033 as used by the manufacturer.
- **Cost of anemia:** Based on an abstract by Lachaine et al.[14] that indicated 17.7% of patients required erythropoietin, CDR assigned a cost of anemia that was 17.7% of the cost used by the manufacturer: 0.177 x $8,304 = $1,470.

4.1 Genotype 1, Treatment-Naive, Non-cirrhotic

CDR reanalysis that varied treatment-related disutility and cost of anemia had only a small impact on the original results (Table 26 to Table 29 in Appendix 4). In all reanalyses, OBV/PTV/RTV and DSV dominated SOF + PR and LDV/SOF.

However, the comparative cost-effectiveness of OBV/PTV/RTV and DSV and LDV/SOF is unstable because the incremental costs and outcomes are very small. Considering that the incremental QALYs of OBV/PTV/RTV and DSV versus SOF/LDV was minimal (0.01 QALY over 70 years) and that results will be sensitive to variations in drug prices, CDR conducted a scenario analysis to assess the impact of potential price reductions on the comparative cost-effectiveness of both drugs.

As shown in Table 2, CDR assessed what would be the most cost-effective option — between no treatment, OBV/PTV/RTV and DSV, and LDV/SOF — for various willingness-to-pay thresholds, based on several price reduction scenarios. At the currently submitted price of OBV/PTV/RTV and DSV, a 20% price reduction of LDV/SOF would result in LDV/SOF being the most cost-effective option, assuming a willingness-to-pay threshold between $43,553 and $938,208 per QALY. If both OBV/PTV/RTV and DSV and LDV/SOF prices are reduced by 20%, OBV/PTV/RTV and DSV is the most cost-effective treatment, assuming a willingness-to-pay threshold > $42,861 per QALY.

TABLE 2: USING THE LOWER ANEMIA COSTS AND PR DISUTILITY SCENARIO, HOW DO THE COST-EFFECTIVE RANGES DIFFER BY VARIATIONS IN PRICE IN TREATMENT-NAIVE, NON-CIRRHOTIC PATIENTS?

Price Reduction		Over What ICUR Range is Each Option Cost-Effective?		
LDV/SOF	OBV/PTV/RTV and DSV	No Treatment	OBV/PTV/RTV and DSV	LDV/SOF
0% ($797.62[a])	0% ($[redacted])	< $55,934 per QALY	> $55,934 per QALY	
0% ($797.62)	20% ($[redacted])	< $42,934 per QALY	> $42,934 per QALY	
0% ($797.62)	40% ($[redacted])	< $29,648 per QALY	> $29,648 per QALY	
20% ($638.10)	0% ($[redacted])	< $43,553 per QALY	> $938,208 per QALY	$43,553 to $938,208 per QALY
20% ($638.10)	20% ($[redacted])	< $42,861 per QALY	> $42,861 per QALY	
20% ($638.10)	40% ($[redacted])	< $29,681 per QALY	> $29,681 per QALY	

Price Reduction		Over What ICUR Range is Each Option Cost-Effective?		
LDV/SOF	OBV/PTV/RTV and DSV	No Treatment	OBV/PTV/RTV and DSV	LDV/SOF
40% ($478.57)	0% ($[redacted])	< $30,401 per QALY	> $1,930,764 per QALY	$30,401 to $1,930,764 per QALY
40% ($478.57)	20% ($[redacted])	< $30,291 per QALY	> $947,560 per QALY	$30,291 to $947,560 per QALY
40% ($478.57)	40% ($[redacted])	< $29,664 per QALY	> $29,664 per QALY	

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year.
[a] The manufacturer used a unit cost of $797.62 for LDV/SOF, which is the same price as the list price of LDV/SOF on the Yukon formulary.

4.2 Genotype 1, Treatment-Naive, Cirrhotic

CDR reanalysis that varied treatment-related disutility and cost of anemia had only a small impact on the original results. In all reanalyses, OBV/PTV/RTV and DSV produced slightly fewer QALYs, but was less costly than LDV/SOF.

However, the comparative cost-effectiveness of OBV/PTV/RTV and DSV and LDV/SOF is unstable and will be sensitive to variation in drug prices. CDR conducted a scenario analysis to assess the impact of potential price reductions on the comparative cost-effectiveness of both drugs.

As shown in Table 3, CDR assessed what would be the most cost-effective option between no treatment, OBV/PTV/RTV and DSV, and LDV/SOF for various willingness-to-pay thresholds, based on several price reduction scenarios. At the currently submitted price of OBV/PTV/RTV and DSV, a 20% price reduction of LDV/SOF would result in LDV/SOF being the most cost-effective option. If both OBV/PTV/RTV and DSV and LDV/SOF prices are reduced by 20%, OBV/PTV/RTV and DSV is the most cost-effective option for a willingness-to-pay threshold between $8,009 and $442,623 per QALY.

TABLE 3: USING THE LOWER ANEMIA COSTS AND PR DISUTILITY SCENARIO, HOW DO THE COST-EFFECTIVE RANGES DIFFER BY VARIATIONS IN PRICE IN TREATMENT-NAIVE, CIRRHOTIC PATIENTS?

Price Reduction		Over What ICUR Range is Each Option Cost-Effective?		
LDV/SOF	OBV/PTV/RTV and DSV	No Treatment	OBV/PTV/RTV and DSV	LDV/SOF
0% ($797.62[a])	0% ($[redacted])	< $13,630 per QALY	$13,630 to $555,655 per QALY	> $555,655 per QALY
0% ($797.62)	20% ($[redacted])	< $7,924 per QALY	$7,924 to $1,212,962 per QALY	> $1,212,962 per QALY
0% ($797.62)	40% ($[redacted])	< $2,452 per QALY	$2,452 to $1,930,279 per QALY	> $1,930,279 per QALY
20% ($638.10)	0% ($[redacted])	< $12,052 per QALY		> $12,052 per QALY
20% ($638.10)	20% ($[redacted])	< $8,009 per QALY	$8,009 to $442,623 per QALY	> $442,623 per QALY
20% ($638.10)	40% ($[redacted])	< $2,551 per QALY	$2,551 to $1,126,099	> $1,126,099 per QALY

Price Reduction		Over What ICUR Range is Each Option Cost-Effective?		
LDV/SOF	OBV/PTV/RTV and DSV	No Treatment	OBV/PTV/RTV and DSV	LDV/SOF
			per QALY	
40% ($478.57)	0% ($[redacted])	< $5,426 per QALY		> $5,426 per QALY
40% ($478.57)	20% ($[redacted])	< $5,538 per QALY		> $5,538 per QALY
40% ($478.57)	40% ($[redacted])	< $2,886 per QALY	> $2,886 per QALY	

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year.
[a] The manufacturer used a unit cost of $797.62 for LDV/SOF, which is the same price as the list price of LDV/SOF on the Yukon formulary.

4.3 Genotype 1, Treatment-Experienced

CDR reanalysis that varied treatment-related disutility and cost of anemia in the three subgroups (null responders, partial responders, and relapsers) had minor impact on the original results: OBV/PTV/RTV and DSV continued to either dominate LDV/SOF or generate fewer QALYs at a lower cost (Table 34 to Table 39 in Appendix 4).

5. ISSUES FOR CONSIDERATION

5.1 Impact of HCV Differential Reinfection Rates on Cost-Effectiveness of Interferon-Free Regimens

A recent literature review by the Ontario HIV Treatment Network identified one meta-analysis reporting pooled estimates of HCV reinfection among people who use drugs and who have been successfully treated for HCV or spontaneously cleared the virus.[16,17] Across the five prospective cohort studies in this meta-analysis, the pooled risk of reinfection was 2.4 (95% confidence interval [CI], 0.9 to 6.1) per 100 person-years (note that the manufacturer assumed a 1% reinfection rate in its model). Given the favourable tolerance profile of interferon-free regimens, acceptance of therapy and willingness to receive a second course of therapy in case of reinfection might be greater than with PR-based regimens.

CDR performed a threshold analysis to assess at what rate of reinfection would OBV/PTV/RTV and DSV no longer dominate SOF + PR in treatment-naive non-cirrhotic patients. When assuming a 1% reinfection rate with SOF + PR and a 3% reinfection rate with interferon-free regimens (OBV/PTV/RTV and DSV and LDV/SOF), CDR found that SOF + PR was the most cost-effective option (ICUR of $68,522 per QALY versus no treatment), while LDV/SOF and OBV/PTV/RTV and DSV were dominated and extendedly dominated, respectively (Table 40 in Appendix 4).

It should be noted that the model assumed no capacity for re-treatment. The comparative cost-effectiveness of drugs assuming different reinfection rates with re-treatment upon reinfection remains unknown.

6. PATIENT INPUT

Input was received by four patient groups: the Canadian Treatment Action Council, the Pacific Hepatitis C Network, Hepatitis C Education and Prevention Society (HepCBC), and the Canadian Liver Foundation. 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 are therefore ineligible for interferon-based regimens. Risk of specific AEs (anemia, depression, rash, neutropenia, and thrombocytopenia) and their related costs were considered in the economic model submitted by the manufacturer.

7. CONCLUSIONS

A number of limitations were identified with the manufacturer's economic submission. The model structure and many of the parameters were not drawn from the best available evidence; however, these issues likely affect comparators and OBV/PTV/RTV and DSV equally. That said, the estimates of absolute costs and QALYs should be viewed with caution. This is important if decision-makers are interested in the cost-effectiveness of interferon-free CHC therapies compared with no active treatment — a treatment option that patients may choose in preference to interferon-comparing regimens. For this comparison, the absolute benefit of the interferon-free regimens will drive the expected cost-effectiveness.

The evidence submitted suggests that OBV/PTV/RTV and DSV leads to similar QALYs compared with LDV/SOF. The ICUR of OBV/PTV/RTV and DSV versus LDV/SOF was sensitive to variations in drug price. As well, OBV/PTV/RTV and DSV is likely to lead to ICURs within commonly accepted thresholds versus other comparators in those patients who would currently receive PR therapy, although ICURs were sensitive to variations in drug prices and were based on naive indirect comparison of efficacy and safety. As such, there is significant uncertainty regarding the comparative cost-effectiveness of OBV/PTV/RTV and DSV compared with other treatment regimens.

The submitted analyses do not provide insight into the likely cost-effectiveness of OBV/PTV/RTV and DSV in other patient groups, such as community-dwelling patients (patients screened for HCV in a non-clinical setting) or patients who would currently be managed with watchful waiting.

APPENDIX 1: COST COMPARISON

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

TABLE 4: COST COMPARISON TABLE FOR DRUGS FOR CHRONIC HEPATITIS C, GENOTYPE 1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
OBV/PTV/RTV and DSV	**12.5 mg/ 75 mg/ 50 mg** **250 mg**	**Tab**	[redacted][a]	**25 mg/ 150 mg/ 100 mg OBV/PTV/RTV once daily and 250 mg DSV twice daily**	**12 weeks[b]**	[redacted]	[redacted]
OBV/PTV/RTV and DSV plus RBV	**12.5 mg/ 75 mg/ 50 mg** **250 mg**	**Tab**	[redacted][a]	**As above, plus 1,000 mg to 1,200 mg/day RBV**	**12 weeks to 24 weeks[b]**	[redacted] **to** [redacted]	[redacted] **to** [redacted]
	200 mg 400 mg 600 mg		**0.0000[a]**			**0[a]**	
Interferon-free regimens							
Ledipasvir/ Sofosbuvir (Harvoni)	90 mg/ 400 mg	Tab	797.62[d]	90 mg/400 mg once daily	8 weeks to 24 weeks[e]	44,667 (8 weeks) 67,000 to 134,000 (12 weeks to 24 weeks)	44,667 (8 weeks) 67,000 to 134,000 (12 weeks to 24 weeks)
Direct-acting antivirals in combination with PR therapy							
SOF (Sovaldi) + PR	400 mg	Tab	654.7619	400 mg once daily	12 weeks[f]	55,000	59,750
	180 mcg/ 200 mg	Vial/ Tabs	395.8400	peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day[g]	12 weeks	4,750	

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
SOF (Sovaldi) + RBV	400 mg	Tab	654.7619	400 mg once daily	24 weeks	110,000	116,090 to 117,308
	400 mg 600 mg	Tab	14.5000[c] 21.7500[c]	1,000 mg to 1,200 mg daily	24 weeks	6,090 to 7,308	
SIM (Galexos) + PefIFN/RBV	150 mg	Cap	434.5500	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 mg to 1,200 mg/day[g]	24 weeks to 48 weeks	9,500 to 19,000	
TEL (Incivek) + PR (discontinued)	375 mg	Tab	69.3810	3 x 375 mg two times daily	12 weeks	34,968	44,468 to 53,968
	180 mcg/ 200 mg	Vial/ Tabs	395.8400	peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day[g]	24 weeks to 48 weeks	9,500 to 19,000	
BOC (Victrelis) + PR	200 mg	Cap	12.5000	4 x 200 mg three times daily	24 weeks 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 mg to 1,400 mg/day	28 weeks to 48 weeks	12,165 to 20,855	
BOC/ peg-IFN alpha-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[h] 2652.55[h] 2726.00[h] 2726.00[h]	BOC 800 mg three times daily; peg-IFN 1.5 mcg/ kg/week; RBV 800 mg to 1,400 mg/day	24 weeks to 44 weeks	31,831 to 59,972	31,831 to 59,972
PR therapy							
peg-IFN alpha-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 mg to 1,200 mg/day[e]	24 weeks to 48 weeks	9,500 to 19,000	9,500 to 19,000
peg-IFN alpha-2b plus RBV (Pegetron)	50 mcg/ 200 mg	2 Vials + 56 Caps	786.3900	peg-IFN 1.5 mcg/ kg/week; RBV 800 mg to 1,400 mg/day[e]	24 weeks to 48 weeks	9,437 to 18,873	9,437 to 18,873
	150 mcg/ 200 mg	2 Vials + 84 Caps 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 Caps to 98 Caps	786.3900 786.3900 868.9600 868.9600			9,437 to 20,855	9,437 to 20,855

BOC = boceprevir; CHC = chronic hepatitis C; DSV = dasabuvir; HCV = hepatitis C virus; IU = international unit; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; peg-IFN = pegylated interferon; PR = pegylated interferon and ribavirin; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
Source: Saskatchewan Drug Benefit (February 2015) prices unless otherwise stated.
[a] Manufacturer's confidential submitted price for a one-day supply of OBV/PTV/RTV and DSV. The manufacturer indicated that stand-alone ribavirin (Moderiba) will be provided by AbbVie Canada Inc. free of charge in combination with OBV/PTV/RTV and DSV when required.
[b] Twelve weeks of OBV/PTV/RTV and DSV alone for patients with genotype 1b without cirrhosis; 12 weeks of OBV/PTV/RTV and DSV plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks of OBV/PTV/RTV and DSV plus RBV for patients with genotype 1a with cirrhosis who had previous null response to peg-IFN and RBV.
[c] Quebec Provincial Drug Formulary price of Ibavyr (February 2015). SOF in combination with RBV (as a stand-alone 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.
[d] Yukon Drug Formulary (March 2015).
[e] Twelve weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. Eight weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than six million IU/mL.
[f] Twelve weeks for genotype 1, 2, and 4; 16 weeks to 24 weeks for genotype 3.
[g] Dosing varies by weight and HCV genotype.
[h] Ontario Drug Benefit Formulary (March 2015).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

Subgroup: Genotype 1 (GT), Treatment-Naive (Interferon-Eligible), Initial Fibrosis Status: 62.6% Mild, 24.4% Moderate, 11% Compensated Cirrhosis, Age = 52, 60% Male, 66.4% GT1a

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO LDV/SOF?

OBV/PTV/RTV and DSV vs. LDV/SOF	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	OBV/PTV/RTV and DSV dominates					

CE = cost-effectiveness; DSV = dasabuvir; LDV/SOF: ledipasvir/sofosbuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir.
Source: Based on manufacturer's base case.

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

OBV/PTV/RTV and DSV vs. 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	OBV/PTV/RTV and DSV dominates					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; SOF = sofosbuvir.
Source: Based on manufacturer's base case.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO SIM + PR?

OBV/PTV/RTV and DSV vs. SIM + PR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone						X
Clinical outcomes		X				

OBV/PTV/RTV and DSV vs. SIM + PR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Quality of life	X					
Incremental CE ratio or net benefit calculation	$17,003 per QALY $26,424 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.
Source: Based on manufacturer's base case.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO BOC + PR?

OBV/PTV/RTV and DSV vs. BOC + 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	$26,699 per QALY $44,303 per life-year					

BOC = boceprevir; CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO TEL + PR?

OBV/PTV/RTV and DSV vs. TEL + 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	$19,196 per QALY $32,500 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; TEL = telaprevir.
Source: Based on manufacturer's base case.

Subgroup: GT1, Treatment-Experienced Null Responders (Interferon-Eligible), Initial Fibrosis Status: 47.3% Mild, 23.3% Moderate, 29.4% Compensated Cirrhosis, Age = 54, 63% Male, 66.4% GT1a

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO LDV/SOF?

OBV/PTV/RTV and DSV vs. LDV/SOF	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	$(1,546,586) per QALY $(994,550) per life-year					

CE = cost-effectiveness; DSV = dasabuvir; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO TEL + PR?

OBV/PTV/RTV and DSV vs. TEL + 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	$6,600 per QALY $10,414 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; TEL = telaprevir.
Source: Based on manufacturer's base case.

Subgroup: GT1, Treatment-Experienced Partial Responders (Interferon-Eligible), Initial Fibrosis Status: 47.3% Mild, 23.3% Moderate, 29.4% Compensated Cirrhosis, Age = 54, 63% Male, 66.4% GT1a

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO LDV/SOF?

OBV/PTV/RTV and DSV vs. LDV/SOF	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone						X
Clinical outcomes		X				
Quality of life		X				

OBV/PTV/RTV and DSV vs. LDV/SOF	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Incremental CE ratio or net benefit calculation	OBV/PTV/RTV and DSV dominates					

CE = cost-effectiveness; DSV = dasabuvir; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 13: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO BOC + PR?

OBV/PTV/RTV and DSV vs. BOC + 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	OBV/PTV/RTV and DSV dominates					

BOC = boceprevir; CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 14: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO TEL + PR?

OBV/PTV/RTV and DSV vs. TEL + 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	OBV/PTV/RTV and DSV dominates					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; TEL = telaprevir.
Source: Based on manufacturer's base case.

Subgroup: GT1, Treatment-Experienced Prior Relapsers (Interferon-Eligible), Initial Fibrosis Status: 47.3% Mild, 23.3% Moderate, 29.4% Compensated Cirrhosis, Age = 54, 63% Male, 66.4% GT1a

TABLE 15: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO LDV/SOF?

OBV/PTV/RTV and DSV vs. LDV/SOF	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	$(2,128,577) per QALY $(1,528,950) per life-year					

CE = cost-effectiveness; DSV = dasabuvir; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 16: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO SIM + PR?

OBV/PTV/RTV and DSV vs. 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	$18,086 per QALY $18,589 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir.
Source: Based on manufacturer's base case.

TABLE 17: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO BOC + PR?

OBV/PTV/RTV and DSV vs. BOC + 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	$1,773 per QALY $1,793 per life-year					

BOC = boceprevir; CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 18: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO TEL + PR?

OBV/PTV/RTV and DSV vs. TEL + 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	$16,011 per QALY $16,064 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; TEL = telaprevir.
Source: Based on manufacturer's base case.

Subgroup: GT1, Treatment-Experienced Overall (Interferon-Eligible), Initial Fibrosis Status: 47.3% Mild, 23.3% Moderate, 29.4% Compensated Cirrhosis, Age = 54, 63% Male, 66.4% GT1a

TABLE 19: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO LDV/SOF?

OBV/PTV/RTV and DSV vs. LDV/SOF	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	$(–2,731,615) per QALY $(–1,268,050) per life-year					

CE = cost-effectiveness; DSV = dasabuvir; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.
Source: Based on manufacturer's base case.

TABLE 20: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OBV/PTV/RTV AND DSV RELATIVE TO TEL + PR?

OBV/PTV/RTV and DSV vs. TEL + 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	$6,268 per QALY $7,070 per life-year					

CE = cost-effectiveness; DSV = dasabuvir; NA = not applicable; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; TEL = telaprevir.
Source: Based on manufacturer's base case.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 21: 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"*			

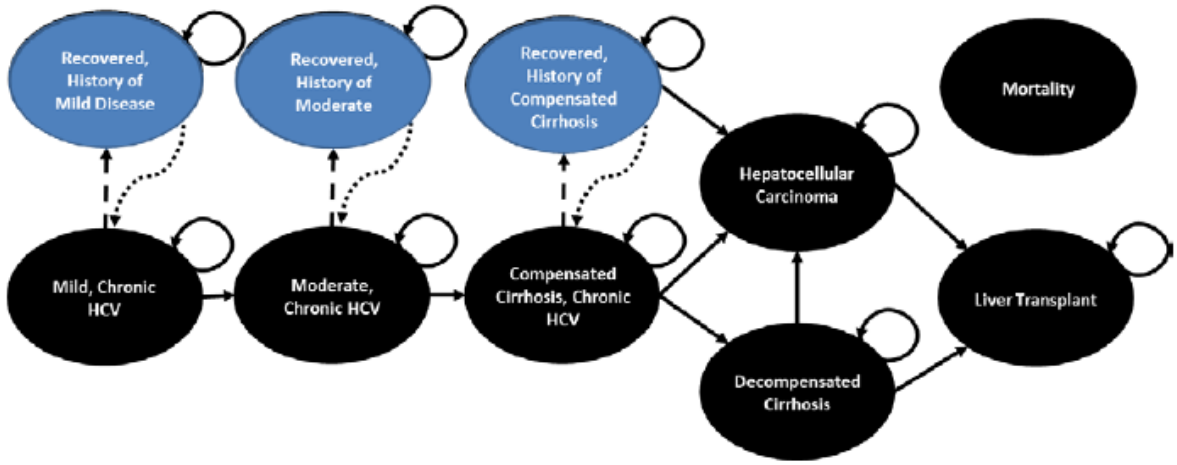
TABLE 22: AUTHOR INFORMATION

Authors	Affiliations		
	Medicus Economics LLC		
	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 4: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



HCV = hepatitis C virus.
Source: Manufacturer's pharmacoeconomic submission.[4]

2. Data Sources

TABLE 23: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Active groups of the pivotal trials for the 5 therapies being evaluated (naive indirect comparison).	The implicit assumption that the trials are comparable in terms of the patients recruited and the potentially extensive but unknown confounding factors for disease progression is a concern.
Natural history	To convert the results in Thein et al. (2008) to transitional probabilities in the manufacturer's mild, moderate, and compensated cirrhotic health state framework, the manufacturer used the Solver function in Excel to calibrate the probabilities so that a 100% mild population (in the same cohort) would have 16% prevalence of cirrhosis at 20 years. Brady et al. (2007)[7] and Krahn et al. (2005).[9]	Ideally, the model would have considered the cost-effectiveness of OBV/PTV/RTV and DSV in the range of patient populations reported by Thein et al.[6] (within the community, clinics, etc.).
Utilities	Brady et al. 2007[7] for health states; disutility of SOF + PR treatment from Younossi et al. 2014[13] conference poster, sensitivity analysis using Hsu et al. 2012.[18]	The authors did not use the EQ-5D-5L utility data available from their clinical trial program for the base-case analysis. These data are based upon a much larger sample of patients (n > 2,000 compared with n = 157 for Brady et al.).

Data Input	Description of Data Source	Comment
Resource use	Brady et al. (2007)[7] and Krahn et al. (2005)[9]	The Krahn et al.[9] model draws upon older US data. It is unlikely that US patterns of care or unit costs are appropriate models for Canadian practice.
AEs	Active groups of the pivotal trials for the 5 therapies being evaluated.	Naive indirect comparison. Definition and severity may vary across trials.
Costs		
• Drug	Wholesale Price Delta PA database	
• AEs • Anemia • Depression • Rash • Neutropenia • Thrombocytopenia	Lachaine et al. (2014)[11,12]	The cost of anemia was likely overestimated as the only case finding necessitated use of erythropoietin.
• Health state	Brady et al. (2007)[7] and Krahn et al. (2005)[9]	

AE = adverse event; DSV = dasabuvir; EQ-5D = EuroQol 5-Dimensions Questionnaire; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

3. Manufacturer's Key Assumptions

TABLE 24: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
It is appropriate to compare unadjusted SVR rates and adverse events across hepatitis C trials.	Likely inappropriate because of unknown confounders in the characteristics of the patients in the trials of the different therapies.
Patients with mild fibrosis and moderate fibrosis have similar SVR rates.	This assumption may not be accurate.
Reinfection rate is 1% per year.	Clinical expert opinion. The true reinfection rate is unknown and is it reasonable to expect that this is likely to differ across patient subgroups. A meta-analysis reported a pooled risk of reinfection of 2.4 (95% CI, 0.9 to 6.1) per 100 person-years among drug users.[17]
Natural history and progression of clinic population is representative of the full population of potential users of OBV/PTV/RTV and DSV.	Likely inappropriate as it targets only one of the natural history trajectories reported by Thein et al. (2008),[6] and the other possible trajectories would likely have a substantial impact upon the results. For example, for the community population, Thein et al. (2008) report that approximately 6% of patients would reach cirrhosis by 20 years compared with the approximately 16% figure picked by the manufacturer.

CI = confidence interval; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; SVR = sustained virologic response.

4. Manufacturer's Results

Table 25 reports the summary of the manufacturer's base-case analyses of the cost-effectiveness of different OBV/PTV/RTV and DSV therapies in a range of patient populations.

TABLE 25: MANUFACTURER'S BASE-CASE RESULTS

Indication	ICUR OBV/PTV/RTV and DSV vs. LDV/SOF ($/QALY)	ICUR OBV/PTV/RTV and DSV vs. SOF + PR ($/QALY)	ICUR OBV/PTV/RTV and DSV vs. SIM + PR ($/QALY)	ICUR OBV/PTV/RTV and DSV vs. BOC + PR ($/QALY)	ICUR OBV/PTV/RTV and DSV vs. TEL + PR ($/QALY)
Treatment-naive GT1	Dominant	Dominant	$17,003	$26,699	$19,196
Null responder GT1	($1,546,586)[a]	TBD	TBD	TBD	$6,600
Partial responder GT1	Dominant	TBD	TBD	Dominant	Dominant
Prior relapser GT1	($2,128,577)[a]	TBD	$18,086	$1,773	$16,011
Treatment-experienced (overall) GT1	($2,731,615)[a]	TBD	TBD	TBD	$6,268

BOC = boceprevir; DSV = dasabuvir; GT1 = genotype 1; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TBD = to be determined because cannot be assessed with current available data; TEL = telaprevir.

[a] Indicates that numerator and denominator are both negative (less costly, fewer QALY gains), causing an inversion in the ratio interpretation.

Source: Manufacturer's pharmacoeconomic submission.[4]

5. CADTH Common Drug Review Reanalysis

Many of the concerns detailed above cannot be addressed through simple correction of parameter values used, as they are driven by structural problems with the model or fundamental problems with the evidence base. However, the CADTH Common Drug Review (CDR) performed a number of reanalyses to demonstrate the impact of correcting the anemia cost and the utility decrement for pegylated interferon and ribavirin (PR) treatment regimens. CDR also provided incremental cost-utility ratios (ICURs) based upon the probabilistic analysis, with 10,000 runs. CDR focused on the comparison of ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) and dasabuvir (DSV) with ledipasvir/sofosbuvir (LDV/SOF) and sofosbuvir plus pegylated interferon and ribavirin (SOF + PR).

- **Treatment-related disutility with SOF + PR:** There is no evidence to justify why patients on SOF + PR would experience a greater utility decrement during treatment (0.145) compared with patients receiving SIM + PR (0.081). CDR applied a utility decrement for SOF + PR of 0.081. Annualized: 0.081 x (12/52) = 0.019 instead of 0.033 as used by the manufacturer.
- **Cost of anemia:** Based on an abstract by Lachaine et al.[14] that indicated 17.7% of patients required erythropoietin, CDR assigned a cost of anemia that was 17.7% of the cost used by the manufacturer: 0.177 x $8,304 = $1,470.

Genotype 1, Treatment-Naive, Non-Cirrhotic

TABLE 26: TREATMENT-NAIVE, NON-CIRRHOTIC PATIENTS — ORIGINAL ASSUMPTIONS BASED UPON THE PROBABILISTIC ANALYSIS, WITH 10,000 RUNS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$11,669.70	10.51	BASELINE			
SOF + PR	$66,004.70	11.27	Dominated			
LDV/SOF	$59,577.13	11.34	Dominated			
OBV/PTV/RTV and DSV	$59,387.72	11.35	Versus no treatment	$47,718.03	0.85	$56,349 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 27: TREATMENT-NAIVE, NON-CIRRHOTIC PATIENTS — LOWER ANEMIA COSTS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$11,844.93	10.52	BASELINE			
SOF + PR	$64,566.20	11.28	Dominated			
LDV/SOF	$59,517.82	11.35	Dominated			
OBV/PTV/RTV and DSV	$59,132.81	11.36	Versus no treatment	$47,287.88	0.85	$55,761 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 28: TREATMENT-NAIVE, NON-CIRRHOTIC PATIENTS — ALTERNATE TREATMENT-RELATED UTILITY DECREMENTS FOR SOF + PR

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$11,853.07	10.52	BASELINE			
SOF + PR	$66,002.26	11.30	Dominated			
LDV/SOF	$59,571.85	11.36	Dominated			
OBV/PTV/RTV and DSV	$59,397.45	11.37	Versus no treatment	$47,544.38	0.85	$56,069 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 29: TREATMENT-NAIVE, NON-CIRRHOTIC PATIENTS — LOWER ANEMIA COSTS AND ALTERNATE TREATMENT-RELATED UTILITY DECREMENTS FOR SOF + PR

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$11,790.39	10.51	BASELINE			
SOF + PR	$64,564.46	11.29	Dominated			
LDV/SOF	$59,533.42	11.35	Dominated			
OBV/PTV/RTV and DSV	$59,129.02	11.36	Versus no treatment	$47,338.63	0.85	$55,934 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

Genotype 1, Treatment-Naive, Cirrhotic

TABLE 30: TREATMENT-NAIVE, CIRRHOTIC PATIENTS — ORIGINAL ASSUMPTIONS BASED UPON THE PROBABILISTIC ANALYSIS, WITH 10,000 RUNS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$46,433.34	7.86	BASELINE			
SOF + PR	$84,402.07	9.59	Dominated			
OBV/PTV/RTV and DSV	$74,304.51	9.92	Versus no treatment	$27,871.17	2.05	$13,566 per QALY
LDV/SOF	$84,524.02	9.94	Versus OBV/PTV/RTV and DSV	$10,219.51	0.02	$543,329 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALYs = quality-adjusted life-years; SOF + PR = sofosbuvir plus pegylated interferon plus ribavirin.

TABLE 31: TREATMENT-NAIVE, CIRRHOTIC PATIENTS — LOWER ANEMIA COSTS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$46,121.94	7.86	BASELINE			
SOF + PR	$82,970.62	9.57	Dominated			
OBV/PTV/RTV and DSV	$73,799.95	9.90	Versus no treatment	$27,678.01	2.04	$13,555 per QALY
LDV/SOF	$84,513.65	9.92	Versus OBV/PTV/RTV and DSV	$10,713.70	0.02	$570,033 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 32: TREATMENT-NAIVE, CIRRHOTIC PATIENTS — ALTERNATE TREATMENT-RELATED UTILITY DECREMENTS FOR SOF + PR

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$46,369.22	7.86	BASELINE			
SOF + PR	$84,615.67	9.60	Dominated			
OBV/PTV/RTV and DSV	$74,570.10	9.92	Versus no treatment	$28,200.88	2.05	$13,727 per QALY
LDV/SOF	$84,795.86	9.94	Versus OBV/PTV/RTV and DSV	$10,225.77	0.02	$542,217 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 33: TREATMENT-NAIVE, CIRRHOTIC PATIENTS — LOWER ANEMIA COSTS AND ALTERNATE TREATMENT-RELATED UTILITY DECREMENTS FOR SOF + PR

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$46,357.52	7.87	BASELINE			
SOF + PR	$83,168.16	9.58	Dominated			
OBV/PTV/RTV and DSV	$74,004.35	9.90	Versus no treatment	$27,646.84	2.03	$13,630 per QALY
LDV/SOF	$84,714.97	9.92	Versus OBV/PTV/RTV and DSV	$10,710.62	0.02	$555,655 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

Genotype 1, Treatment-Experienced, Null Responders

TABLE 34: TREATMENT-EXPERIENCED, NULL RESPONDERS — ORIGINAL ASSUMPTIONS BASED UPON THE PROBABILISTIC ANALYSIS, WITH 10,000 RUNS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,145.46	9.31	BASELINE			
OBV/PTV/RTV and DSV	$74,185.68	10.42	Versus no treatment	$53,040.22	1.12	$47,523 per QALY
LDV/SOF	$94,080.09	10.44	Versus OBV/PTV/RTV and DSV	$19,894.41	0.01	$1,482,811 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-years.

TABLE 35: TREATMENT-EXPERIENCED, NULL RESPONDERS — LOWER ANEMIA COSTS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,315.67	9.31	BASELINE			
OBV/PTV/RTV and DSV	$73,849.05	10.42	Versus no treatment	$52,533.38	1.11	$47,186 per QALY
LDV/SOF	$94,091.83	10.43	Versus OBV/PTV/RTV and DSV	$20,242.78	0.01	$1,566,824 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.

Genotype 1, Treatment-Experienced, Partial Responders

TABLE 36: TREATMENT-EXPERIENCED, PARTIAL RESPONDERS — ORIGINAL ASSUMPTIONS BASED UPON THE PROBABILISTIC ANALYSIS, WITH 10,000 RUNS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,358.54	9.32	BASELINE			
LDV/SOF	$94,046.11	10.46	Dominated			
OBV/PTV/RTV and DSV	$63,319.81	10.46	Versus no treatment	$41,961.27	1.14	$36,888 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.

TABLE 37: TREATMENT-EXPERIENCED, PARTIAL RESPONDERS — LOWER ANEMIA COSTS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,274.32	9.33	BASELINE			
LDV/SOF	$94,180.57	10.46	Dominated			
OBV/PTV/RTV and DSV	$63,056.03	10.47	Versus no treatment	$41,781.71	1.14	$36,756 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.

Genotype 1, Treatment-Experienced, Relapse

TABLE 38: TREATMENT-EXPERIENCED, RELAPSE — ORIGINAL ASSUMPTIONS BASED UPON THE PROBABILISTIC ANALYSIS, WITH 10,000 RUNS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,328.50	9.31	BASELINE			
OBV/PTV/RTV and DSV	$63,591.25	10.42	Versus no treatment	$42,262.75	1.11	$38,037 per QALY
LDV/SOF	$94,174.16	10.44	Versus OBV/PTV/RTV and DSV	$30,582.91	0.01	$2,040,588 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.

TABLE 39: TREATMENT-EXPERIENCED, RELAPSE — LOWER ANEMIA COSTS

Decision Option	Expected Outcomes		Incremental Cost-Effectiveness			
	Costs	QALYs	Comparator	Incr. Costs	Incr. QALYs	ICUR
No treatment	$21,153.51	9.31	BASELINE			
OBV/PTV/RTV and DSV	$63,161.54	10.43	Versus no treatment	$42,008.03	1.11	$37,678 per QALY
LDV/SOF	$94,045.77	10.44	Versus OBV/PTV/RTV and DSV	$30,884.23	0.02	$1,973,669 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; QALY = quality-adjusted life-year.

Threshold Analysis on Reinfection Rate

The manufacturer assumes a 1% annual reinfection rate, based on clinical expert opinion. If differences in reinfection rate exist between populations receiving PR-based regimens versus interferon-free regimens, it is important to understand the threshold upon which OBV/PTV/RTV and DSV would no longer dominate SOF + PR.

When assuming a 1% reinfection rate with SOF + PR and a 3% reinfection rate with interferon-free regimens (OBV/PTV/RTV and DSV and LDV/SOF), CDR found that SOF + PR was the most cost-effective option (ICUR of $68,522 per QALY versus no treatment), while LDV/SOF and OBV/PTV/RTV and DSV were dominated and extendedly dominated, respectively.

TABLE 40: THRESHOLD ANALYSIS ON REINFECTION RATE: ASSUMING 3% REINFECTION RATE FOR INTERFERON-FREE REGIMENS AND 1% FOR PR-BASED REGIMENS

	Costs	QALYs	Comparison	Incremental Cost	Incremental QALY	ICUR
No treatment	$11,793.95	10.51				
LDV/SOF	$60,822.58	11.21	Dominated			
OBV/PTV/RTV and DSV	$60,448.20	11.22	Ext. dominated			
SOF + PR	$64,575.84	11.28	Versus no treatment	$52,781.89	0.77	$68,522 per QALY

DSV = dasabuvir; ICUR = incremental cost-utility ratio; LDV/SOF = ledipasvir/sofosbuvir; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; PR = pegylated interferon and ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

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