Common Drug Review

Pharmacoeconomic Review Report

March 2016

Drug	ombitasvir, paritaprevir, ritonavir (Technivie)
Indication	In combination with ribavirin for the treatment of adults with genotype 4 chronic hepatitis C virus infection without cirrhosis who are either treatment naive or previously treated with peginterferon and ribavirin.
Listing request	As per indication
Dosage form(s)	Ombitasvir/paritaprevir/ritonavir film-coated tablets (12.5/75/50 mg) for oral administration
NOC date	20 October 2015
Manufacturer	AbbVie Corporation

Note: At the time of the CADTH Common Drug Review submission for Technivie, the price submitted by the manufacturer to CADTH was confidential. However, the manufacturer advised during the review that the submitted price does not need to remain confidential.

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
LDV	ledipasvir
OBV	ombitasvir
PR	pegylated interferon plus ribavirin
PTV	paritaprevir
QALY	quality-adjusted life-year
RBV	ribavirin
RTV	ritonavir
SOF	sofosbuvir
SVR	sustained virologic response

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV)
Study Question	What is the cost-effectiveness of OBV/PTV/RTV in the treatment of naive or experienced patients without cirrhosis (METAVIR F0 to F3) with genotype 4 chronic hepatitis C in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with chronic hepatitis C viral infection genotype 4 in the following subgroups: (1) treatment-naive, (2) treatment-experienced with PR
Treatment	OBV/PTV/RTV + RBV oral for 12 weeks
Outcomes	SVR and QALYs
Comparators	• SOF/LDV • SOF + PR • PR
Perspective	Government
Time Horizon	Lifetime horizon (70 years)
Results for Base Case	Treatment-naive patients: • PR is cost-effective up to a willingness-to-pay of $113,324 per QALY. • OBV/PTV/RTV is cost-effective where decision-makers are willing to pay more than $113,324 per QALY. • SOF/LDV and SOF + PR are dominated (less effective and more costly) by OBV/PTV/RTV. Treatment-experienced patients: • PR and SOF + PR were not considered as comparators. • SOF/LDV is dominated (less effective and more costly) by OBV/PTV/RTV. • OBV/PTV/RTV is dominant at all willingness-to-pay values.
Key Limitations	CDR identified a number of limitations with the manufacturer's submission. The two key limitations (with the others detailed within the report) are: • The unknown impact of liver damage caused by the treatment on patients • The uncertainty relating to how long a benefit from being in SVR will last (aside from any benefits from non-progression). Further, the comparative cost-effectiveness of OBV/PTV/RTV and DSV and SOF/LDV is unstable and sensitive to variations in drug price.
CDR Estimates	CDR was unable to undertake reanalyses to address the uncertainty relating to liver damage from the treatment. The base-case analyses, including a no-treatment option contained in the manufacturer's Excel model, suggest that: • Treatment-naive: OBV/PTV/RTV is not cost-effective when compared with PR at an ICUR of $112,909 per QALY. • Treatment-experienced: OBV/PTV/RTV may be marginally cost-effective against a comparator of "no treatment" at an ICUR of $52,346 per QALY. • ICURs for OBV/PTV/RTV were generally higher in the sensitivity analyses considered.

CDR = CADTH Common Drug Review; DSV = dasabuvir; HCV = hepatitis C virus; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response.

EXECUTIVE SUMMARY

Background

Ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/RTV + RBV) fixed-dose combination is an all-oral interferon-free regimen indicated for the treatment of adults with genotype 4 chronic hepatitis C virus (HCV) infection without compensated cirrhosis, who either are treatment-naive or were previously treated with pegylated interferon plus ribavirin (PR).[1] The recommended dose of OBV/PTV/RTV is two OBV 12.5 mg/PTV 75 mg /RTV 50 mg tablets once daily during 12 weeks. The manufacturer submitted a confidential price of $665 per daily blister (containing two tablets of OBV/PTV/RTV), corresponding to $55,860 for a 12-week treatment.[2]

OBV/PTV/RTV is licensed for use in combination with RBV in patients with HCV genotype 4 infection. AbbVie states that an application has been filed for standalone RBV to be approved and that, if approved, it would be provided by AbbVie Canada free of charge in combination with OBV/PTV/RTV when required.

The manufacturer submitted a cost-utility analysis conducted over a patient lifetime (70 years) from a government-payer perspective.[3] The manufacturer's base-case analyses compared OBV/PTV/RTV with three comparators: sofosbuvir plus ledipasvir (SOF/LDV), sofosbuvir plus PR (SOF + PR), and PR alone. The model consists of nine distinct health states, which reflect different stages of HCV and its complications.

In the base-case analysis, the manufacturer examined the cost-effectiveness of OBV/PTV/RTV in a treatment-naive cohort (composed of 82.6% of patients with mild fibrosis and 17.4% with moderate fibrosis) and in a treatment-experienced cohort (67.3% with mild fibrosis and 32.7% with moderate fibrosis). The manufacturer reported that OBV/PTV/RTV dominates (OBV/PTV/RTV is less costly and more effective) SOF/LDV for treatment-experienced patients. OBV/PTV/RTV is, however, unlikely to be cost-effective when compared with PR for patients who are treatment-naive, with an incremental cost-utility ratio (ICUR) of more than $100,000 per quality-adjusted life-year (QALY).

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) analyses suggest that at the submitted confidential price, OBV/PTV/RTV + RBV is at best only marginally cost-effective versus no treatment for treatment-experienced patients ($52,346 per QALY) — the manufacturer did not consider "no treatment" or PR in its analysis for treatment-experienced patients. OBV/PTV/RTV is unlikely to be cost-effective versus PR in treatment-naive patients ($112,909 per QALY). These findings are conservative, and the true cost-effectiveness of OBV/PTV/RTV is likely higher.

The manufacturer assumes that all patients achieving sustained virologic response will obtain a consistently higher utility than other patients with the same level of fibrosis but with HCV. Evans et al., on which the manufacturer states that it bases its modelling, used a more conservative assumption that this higher utility persists for only one year. Where either a lower benefit is assumed (e.g., an increment of 0.02 versus 0.04 per year) or the benefit is applied in only one year (versus lifetime, while non-progressing), cost-effectiveness is much worse. In the treatment-experienced patients, the estimated ICUR for OBV/PTV/RTV increases from $52,346 to $74,518 (lower utility value) and $116,633 (benefit applied for only one year) per QALY.

The recent warnings regarding liver damage associated with OBV/PTV/RTV have not been incorporated into the analysis, which represents an important limitation. This could not be explored in reanalyses given the information currently available to CDR.

Conclusions

Based on CDR analyses, OBV/PTV/RTV is associated with an ICUR of more than $112,000 when compared with PR in treatment-naive patients and more than $52,000 compared with no treatment in treatment-experienced patients. These results do not account for the possible impact of OBV/PTV/RTV on liver damage; as such, these estimates likely represent an underestimation of the ICURs.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted cost-utility analyses based upon a Markov model that consists of nine distinct health states.[2] The model structure is based on Brady et al. (2007).[4] The schematic for this natural history model is provided in Figure 1 of Appendix IV. All patients are assumed to begin in either a mild fibrosis (METAVIR F0 to F1) or moderate fibrosis (METAVIR F2 to F3) state with hepatitis C virus (HCV) infection. Two further states allow for the possibility of sustained virologic response (SVR) from these two states. Progression is possible from mild to moderate fibrosis and then on to compensated cirrhosis and subsequent, more severe disease.

The model includes states for decompensated cirrhosis, hepatocellular carcinoma, and liver transplant. The final model state is "dead." In contrast with some recent cost-effectiveness analysis models, the submitted analysis allows for reinfection (but assumes no retreatment upon reinfection). Decompensated cirrhosis, hepatocellular carcinoma, and liver transplant have a liver-specific risk of death as well as the all-cause mortality that applies to all other health states.

Within the economic model, the short-term success of the treatments in helping patients achieve SVR — which was the main focus of the trials — is used to identify the impact on progression and hence the distribution of patients within the model's states. By assigning quality of life to each state, quality-adjusted life-years (QALYs) can be formed and the main outcome of the analysis is cost-utility in terms of incremental cost-utility ratios (ICURs). The economic model is based on a simulated natural history derived from the large scale meta-analysis of chronic hepatitis C epidemiology studies reported by Thein et al. (2008)[5] and other sources. The submission authors report that they used the Excel Solver facility to convert the results from Thein et al. to transition probabilities for mild to moderate and moderate 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 manufacturer submitted two cost-utility analyses conducted over a patient lifetime (70 years) from a government-payer perspective. For treatment-naive patients eligible to receive ribavirin (RBV) treatment, the cohort is assumed to have a mean age of 47 at the start of the model with 82.6% of patients in the mild fibrosis state. The manufacturer's base-case analyses compared ombitasvir/paritaprevir/ritonavir plus ribavirin (RBV) (OBV/PTV/RTV + RBV) with three comparators: sofosbuvir plus ledipasvir (SOF/LDV), sofosbuvir plus pegylated interferon plus ribavirin (PR) (SOF + PR), and PR alone. Notably, the manufacturer did not report a watchful-waiting and/or no-treatment comparator even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimes, and data for "no treatment" are included in the model. Functionality to allow "no treatment" to be compared alongside other treatment options appears to have been removed.

In the treatment-experienced case, the patient cohort is assumed to have a mean age of 51 with 67.3% of patients beginning in the mild fibrosis state. In the model, the manufacturer provides a table from Hezode et al. (2015)[6] that suggests that within AbbVie trial data, 23 (47%) of treatment-experienced patients were null responders to prior treatment on PR, nine (18%) had had a partial response, and 17

(35%) had experienced a relapse. Identical data appear to be provided for all three of these groups, so these cannot be considered as separate subgroups in the model. For the treatment-experienced case, only OBV/PTV/RTV + RBV and SOF/LDV are considered as comparators, with "no treatment" again not considered within the model.

Clinical effectiveness is assessed using SVR. SVR data for the OBV/PTV/RTV + RBV regimen were based on the PEARL I trial.[6] For treatment-naive patients, this trial compared 44 patients randomized to receive OBV/PTV/RTV (no RBV) and 42 patients randomized to receive OBV/PTV/RTV + RBV. The second of these arms (42 patients completed treatment) provided SVR data for the treatment-naive group. PEARL I also included 49 treatment-experienced arms assigned to OBV/PTV/RTV + RBV, and these data are used to obtain SVR rates for this group.[6] SVR data for the SOF comparators were obtained from an open-label study (SOF/LDV)[7] and from analysis of the NEUTRINO trial (SOF + PR).[8] The manufacturer considered a range of data sources for SVR rates following PR and selected a small study[9] (n = 13) as this allows inference of a genotype 4 group in the mild and moderate fibrosis states (F0 to F3) of 76.9%. The only alternative study identified with a higher SVR rate on PR treatment (81.8%) had a lower sample size (n = 11) and it is unclear from the manufacturer's submission whether this cohort satisfied the fibrosis criteria for the model.

As with the effectiveness, adverse events rates for five events (anemia, rash, depression, neutropenia, thrombocytopenia) were taken from a variety of sources. As with the clinical evidence, a range of sources are used. For the OBV/PTV/RTV + RBV treatment under consideration, the PEARL I trial was again used.[6] Likewise, the SOF/LDV treatment option again cites the French open-label study[7] as reporting less than 5% complications, although this was assumed to be 0 by the manufacturer due to lack of specific data on which complications arose. For both SOF + PR and PR, adverse events data were used from the studies providing SVR data, but these adverse event rates apply across multiple genotypes as no data specific to genotype 4 were reported.

The quality-of-life data attached to each health state were based on Health Utilities Index Mark 3 data from Brady et al.[4] A potentially critical assumption in the model is that each "recovered" SVR state attracts a 0.04 higher quality-of-life value in every year. In addition, short-term treatment-based EuroQol 5-Dimensions Questionnaire disutilities are also calculated for each of the treatments, and these are converted to QALY gains in the period in which treatment occurs. Small QALY gains were assigned on treatment for OBV/PTV/RTV + RBV based on PEARL I.[6] For SOF/LDV, data from the other PEARL I[6] arm (OBV/PTV/RTV) were used on the basis that this included two direct-acting antiviral therapies. Patients receiving PR-based regimens have lower on-treatment QALYs: 0.03 lower for SOF + PR[10] and 0.10 lower for PR[11] regimens; for the other treatments, the on-treatment "disutility" is negative, and so slightly increases utility.

Health state costs are based primarily on Brady et al.,[4] with these figures converted to 2013 Canadian dollars using the health and personal care component of the Consumer Price Index. Adverse event costs for anemia, rash, and depression were based on Lachaine et al.,[12] with neutropenia and thrombocytopenia costs based on a single medical assessment using Ontario Ministry estimates.[13] (The Lachaine study also estimates the cost of liver transplantations, but these figures are lower than the costs from Brady et al.; these values were not used in the model.)

2. MANUFACTURER'S BASE CASE

As only two subgroups are considered within the manufacturer's submission, a full summary of the evidence is presented. The results from the manufacturer's submission suggest very little uncertainty about the cost-effective option at a willingness-to-pay of around $50,000 per QALY.

The manufacturer's base case presents the deterministic results, rather than an average across the cases considered in the probabilistic sensitivity analysis. Within this analysis, OBV/PTV/RTV + RBV and PR are the only treatments for treatment-naive patients that are potentially cost-effective. The other two treatments considered are dominated by OBV/PTV/RTV + RBV. OBV/PTV/RTV + RBV provides an expected additional 0.30 QALYs over the lifetime of the patient at an expected lifetime cost of $33,668. This corresponds to an ICUR of $113,324 per QALY. If the willingness-to-pay exceeds this amount, then the more expensive treatment would be considered cost-effective.

At a willingness-to-pay of $50,000 per QALY, the data provided in the manufacturer's Excel model suggest a likelihood of 1.6% that the OBV/PTV/RTV + RBV therapy is cost-effective.

TABLE 2: RESULTS OF THE MANUFACTURER'S BASE CASE — TREATMENT-NAIVE PATIENTS

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	Incremental Cost per QALY
PR	(Baseline)	$25,800		11.95		
OBV/PTV/RTV + RBV	PR	$59,468	$33,668	12.25	0.30	$113,324
SOF + PR	OBV/PTV/RTV + RBV	$65,326	$5,868	12.21	–0.04	Dominated
SOF/LDV	OBV/PTV/RTV + RBV	$70,770	$11,302	12.21	–0.04	Dominated

LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.
Note: Options presented in increasing cost order.

For the treatment-experienced cohort, OBV/PTV/RTV + RBV is considered alongside SOF/LDV. In this case, treatment with OBV/PTV/RTV + RBV is suggested to be around $12,400 cheaper per patient in the deterministic analysis. In addition, OBV/PTV/RTV + RBV is also argued to provide approximately 0.13 additional QALYs and is therefore argued to dominate SOF/LDV. The Excel spreadsheet provided by the manufacturer does not include the run of the model that provides these results. However, when this analysis was rerun by CDR, all 500 cases considered support the cost-effectiveness of OBV/PTV/RTV + RBV against SOF/LDV.

TABLE 3: RESULTS OF THE MANUFACTURER'S BASE CASE — TREATMENT-EXPERIENCED PATIENTS

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	Incremental Cost per QALY
PR	Not included					
SOF + PR	Not included					
OBV/PTV/RTV + RBV	(Baseline)	$59,429		11.56		
SOF/LDV	OBV/PTV/RTV + RBV	$71,846	$12,416	11.43	–0.13	Dominated

LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer's submission contains a probabilistic sensitivity analysis and explores sensitivity within a series of scenario analyses. Methodological questions considered include assessing the impact of alternative figures for health utilities and changes in the transition probabilities (using age-dependent probabilities from Grishchenko et al.).[14]

In one case, the changes to the health utility reduced the ICUR between OBV/PTV/RTV + RBV and PR by at least 25%. In this case (Sensitivity 2), the treatment-related "disutility" for OBV/PTV/RTV + RBV is further reduced such that being on-treatment now provides 0.014 additional QALYs, as opposed to 0.002 QALYs in the base case. This is based on an observed difference between baseline and post-treatment values observed at 12 weeks post-treatment in PEARL I[6] (i.e., typically at 24 weeks post-baseline). In this case, the ICUR falls to $52,822 per QALY. Two other health utility scenario analyses also appear to reduce the ICUR to the range of $50,000 to $60,000 per QALY. In both cases, however, this appears to be driven by large increases in the utility difference assigned to achieving SVR, since the values are 365% and 385% of the base case. These alternative assumptions do not appear to be conservative.

The univariate sensitivity analyses suggest that the results are broadly most sensitive to assumptions surrounding SVR rates. A probabilistic sensitivity analysis was also run with 500 iterations, with these results alluded to within the base case above.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Comparators: The manufacturer's submission does not include a watchful-waiting/no-treatment comparator even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimens. In contrast, the Excel model provided appears to allow for this functionality as long as some very simple functionality (e.g., insertion of results) is restored. The lack of a no-treatment option makes the interpretation of results difficult.

- In the case of treatment-naive patients, PR already provides a cheaper, non-dominated alternative, and the only question in the base case would be whether the addition of "no treatment" could result in PR being extended dominated.

- For treatment-experienced patients, however, the comparison of OBV/PTV/RTV + RBV with SOF/LDV means that only two relatively expensive treatments are compared. In this case, a no-treatment option may represent a cost-effective alternative that is not considered within the manufacturer's submission. This is particularly important, given that options providing for PR-containing regimens are not included in the model.

Efficacy inputs are not stratified by fibrosis stages: The efficacy inputs were not stratified by fibrosis stage. It is assumed that the comparative effectiveness of SOF/LDV with other regimens is independent of fibrosis stage, which is likely not the case.

Utility values associated with SVR: The results of the manufacturer's sensitivity analyses suggest that the model is highly sensitive to changes in the benefit assigned to achieving SVR.

- In the base case, the recovered states have a fixed 0.04 utility increment in all years. For example, if the HCV mild state with fibrosis receives the mean value of 0.73, the SVR state with mild fibrosis receives the value 0.77. No uncertainty in this 0.04 difference is included in the probabilistic sensitivity analysis.
- The manufacturer does modify this 0.04 increment in deterministic sensitivity analyses but typically only to increase it. There are also questions about how long any utility benefit from achieving SVR lasts. Brady et al. assume the increment applies only for the year following achieving SVR.[4] It is unclear on what basis the manufacturer assumes that this is a persistent improvement attached to every year in SVR if Brady et al. is cited as the source of this assumption.

Evidence for adverse events: There is a lack of comparative evidence for both the SVR rates and the adverse event rates across the comparators considered. In many cases, the adverse event data were available only across genotypes.

The adverse events in the manufacturer's model were anemia, rash, depression, neutropenia, and thrombocytopenia. Although the trial data presented suggest that each is a relevant side effect, it does not appear that this list comprises all relevant side effects. In particular, there is no specific side effect included that captures the recent indication that OBV/PTV/RTV use was associated with serious liver injury. While the recent Health Canada warning[15] notes that the majority of these cases relate to patients with cirrhosis, the wording suggests that some did not have cirrhosis and would therefore fall within the group covered by this CDR Pharmacoeconomic Review Report. Even if there are no recorded issues, the recommendation for close monitoring of patients (and its attendant costs) does not appear to have been incorporated into the model.

5. CADTH COMMON DRUG REVIEW ANALYSES

For the treatment-naive cohort, the probabilistic sensitivity analysis was replicated using a higher number of model iterations (10,000) and results from the no-treatment comparator contained within the Excel model. For the treatment-naive and treatment-experienced cohorts, the baseline results were confirmed and additional analyses conducted, including:

1. Replacing the manufacturer's assumption (0.04 utility increment for every year in SVR) with a lower figure (0.02)
2. Replacing the manufacturer's assumption (0.04 utility increment for every year in SVR) with the Brady et al. base-case assumption that this increment applies only in the first year[4]
3. A series of price reduction scenarios.

Treatment-Naive Cohort

Both the manufacturer's submission and the CDR reanalysis suggest that OBV/PTV/RTV + RBV will be cost-effective versus PR where willingness-to-pay exceeds about $113,000 per QALY (manufacturer $113,324 per QALY; CDR $112,909 per QALY.) In the two scenarios considering a lower SVR increment, the ICUR between OBV/PTV/RTV + RBV and PR increases to about $141,000 and $181,000 per QALY. This confirms the results of the manufacturer's sensitivity analysis that cost-effectiveness is likely to be sensitive to the assumptions surrounding this increment.

The question of how long any specific utility benefit lasts from attaining SVR appears to be a particularly important question. Where attaining SVR increases utility for only one year, the most cost-effective option at $50,000 per QALY appears to be no treatment, with PR becoming cost-effective only where willingness-to-pay exceeds $65,870 per QALY.

TABLE 4: TREATMENT-NAIVE PATIENTS — UTILITY INCREMENT APPLIES TO FIRST YEAR IN SVR ONLY

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$11,833		11.32		
PR	No treatment	$25,786	$13,953	11.53	0.21	$65,870
OBV/PTV/RTV + RBV	PR	$59,449	$33,663	11.72	0.19	$180,362
SOF + PR	OBV/PTV/RTV + RBV	$65,316	$5,868	11.68	–0.04	Dominated
SOF/LDV	OBV/PTV/RTV + RBV	$70,752	$11,303	11.70	–0.02	Dominated

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; vs. = versus.

Even where the manufacturer's preferred assumption around SVR is used, the ICUR for OBV/PTV/RTV + RBV exceeds $50,000 per QALY.

A series of price reduction scenarios were considered for the model, with each 1% price reduction reducing the ICUR by approximately $560 per QALY. In order to reach $50,000 per QALY, this suggests that a price reduction of 34% would be necessary.

Treatment-Experienced Cohort

For the treatment-experienced cohort, no clinical data were provided for the two PR-based regimens (SOF + PR, PR). In the manufacturer's analysis, only OBV/PTV/RTV + RBV and SOF + LDV are compared. Even with the addition of a no-treatment option in the CDR analysis, this leaves only a small number of possible comparators within the model. In the CDR base-case analysis, OBV/PTV/RTV + RBV dominates SOF + LDV (as claimed by the manufacturers) but the ICUR for OBV/PTV/RTV + RBV versus no treatment is around $52.346 per QALY, as identified in Table 5. In this case, at $50,000 per QALY, OBV/PTV/RTV + RBV has about a 37% likelihood of being a cost-effective option versus no treatment (63%) in the CDR base case, using the manufacturer's parameter distributions (including for no treatment) from the existing Excel model.

In order to obtain an ICUR of $50,000 per QALY, the price scenario analyses suggest that a price reduction of about 4% would be necessary.

TABLE 5: TREATMENT-EXPERIENCED PATIENTS — CADTH COMMON DRUG REVIEW BASE CASE

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$ 12,276		10.59		
OBV/PTV/RTV + RBV	No treatment	$ 59,422	$47,147	11.49	0.90	$52,346
SOF/LDV	OBV/PTV/RTV + RBV	$ 71,816	$12,393	11.36	–0.13	Dominated

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.

Where the manufacturer's assumption around the SVR increment is modified, the ICUR for OBV/PTV/RTV + RBV increases to $74,518 (halved utility benefit from SVR) and $116,633 (utility benefit applies in first SVR-year only). The corresponding likelihood of cost-effectiveness (at $50,000 per QALY) is likewise affected, with this equal to 37% in the modified base case but only 3.8% and 0.4% in the two alternative cases.

6. ISSUES FOR CONSIDERATION

- The impact of the recent Health Canada warning for serious liver injury has not been incorporated into the manufacturer's pharmacoeconomic submission. Depending on the risks that apply for the patient groups considered here, this has the potential to significantly affect the cost-effectiveness of the OBV/PTV/RTV + RBV regimen.
- Patient input received for this submission suggests that patients with genotype 4 chronic hepatitis C look forward to an additional treatment option. The ability to avoid the use of interferon was noted as a "game changer" for some patients; however, some patients were concerned about the need for using RBV in combination with OBV/PTV/RTV. Several patients noted that they were discouraged from seeking treatment because of the continued presence of RBV in contemporary therapy options.

Patients noted the side effects associated with interferon: anemia, sleep loss, depression, mood swings, joint pain, rashes, hearing loss, skin sores, hair loss, headaches, chills, nausea, severe fatigue, and excessive weight loss. Additional medications are often required to manage the side effects associated with interferon. Patients also indicated that they were looking forward to more effective treatment options.

The manufacturer has incorporated adverse events associated with PR into its analysis. Although, as stated previously, effects on the liver with OBV/PTV/RTV + RBV were not explored as part of the analysis.

7. CONCLUSIONS

A small number of potentially important limitations were identified with the manufacturer's economic submission, of which some could be addressed as part of CDR analyses.

For treatment-naive patients, the manufacturer's submission suggests that OBV/PTV/RTV + RBV is not cost-effective at $113,324 per QALY when compared with PR, although it does appear to provide greater effectiveness at higher costs. CDR broadly agrees with this finding, although it is noted that the ICUR may be underestimated given the concerns regarding the use of a yearly SVR increment and liver-related complications that are not incorporated into the existing model. If these latter issues were to be ignored, the price-based analyses suggest that a price reduction of around 34% would be necessary to achieve an ICUR of $50,000 per QALY versus PR.

For treatment-experienced patients, the manufacturer's submission suggests that OBV/PTV/RTV + RBV provides treatment that is more effective and lower cost than SOF/LDV. However, this includes neither the main comparators from the treatment-naive analysis nor a no-treatment option. Although CDR could not include a PR-based regimen, the no-treatment option was included, and OBV/PTV/RTV + RBV was only marginally cost-effective (around $52,000 per QALY) in the base case versus no treatment. Any concerns about either the assumptions around SVR and utility or about liver-related complications would likely prevent OBV/PTV/RTV + RBV from being deemed cost-effective at the submitted current price.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 6 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 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 6: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 4

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Ombitasvir/ paritaprevir/ ritonavir (Technivie) plus RBV	12.5/75/50 mg	2 tabs	665.0000[a]	Two tablets once daily	12 weeks	55,860	55,860
	400 mg 600 mg	tab	0.0001[a]	1,000 to 1,200 mg daily		0[a]	
Interferon-Free Regimens							
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	cap	434.5500	150 mg once daily	12 to 24[b] weeks	36,502 to 73,004	91,502 to 183,004
	400 mg	tab	654.7619	400 mg once daily		55,000 to 110,000	
Direct-Acting Antivirals in Combination With PR Therapy							
Sofosbuvir (Sovaldi) plus PR	400 mg	tab	654.7619	400 mg once daily	12 weeks	55,000	59,793
	180 mcg/200 mg	vial/tab	399.4100	PEG-IFN 180 mcg/week; RBV 800 to 1,200 mg/day		4,793	
Simeprevir (Galexos) plus PR	150 mg	cap	434.5500	150 mg once daily	12 weeks	36,502	46,088 to 55,674
	180 mcg/200 mg	vial/tab	399.4100	PEG-IFN 180 mcg/week; RBV 800 to 1,200 mg/day	24 to 48 weeks[c]	9,586 to 19,172	
PR Therapy							
Peginterferon alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	vial or syringe/ 28 tabs 35 tabs 42 tabs	399.4100	PEG-IFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[d]	48 weeks	19,172	19,172

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Peginterferon alfa-2b + RBV (Pegetron)	50 mcg/200 mg	2 vials + 56 caps	793.4700[e]	PEG-IFN 1.5 mcg/kg/ week; RBV 800 to 1,400 mg/day	48 weeks	19,043	19,043
	150 mcg/200 mg	2 vials + 84 or 98 caps	879.7800[e]			21,115	21,115
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens/ 56 to 98 caps	793.4700 793.4700 876.7800 879.7800			19,043 to 21,115	19,043 to 21,115

PEG-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
Note: All prices are from the Saskatchewan Drug Plan online formulary (Nov 2015) unless otherwise indicated.[16]
[a] Manufacturer's confidential price, submitted as $665.00 per daily dose (i.e., per two tablets). The manufacturer has indicated that RBV would be provided free of charge to patients receiving OBV/PTV/RTV (Technivie). Of note: The Saskatchewan Formulary lists the RBV brand Moderiba at $0.0001 per tablet for patients receiving Holkira Pak, which is from the same manufacturer as OBV/PTV/RTV (Technivie). RBV, if not supplied at no charge, would cost an additional $3,045 to $3,654 per patient per course.
[b] 12 weeks for treatment-naive, prior-relapse patients, or prior non-responders with or without cirrhosis who are not co-infected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.
[c] 24 weeks for treatment-naive or prior-relapse patients with or without cirrhosis without HIV co-infection, or without cirrhosis but with HIV co-infection. 48 weeks for treatment-naive or prior-relapse patients with cirrhosis and HIV co-infection. 48 weeks for prior non-responders with or without cirrhosis and with or without HIV co-infection.
[d] 48 weeks for genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV co-infection.
[e] Ontario Drug Benefit Formulary, Exceptional Access Program (Nov 2015).[17]

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 7: 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"*	References were not complete, with information on data sources not appropriately referenced in the text of the report.		

TABLE 8: AUTHORS' INFORMATION

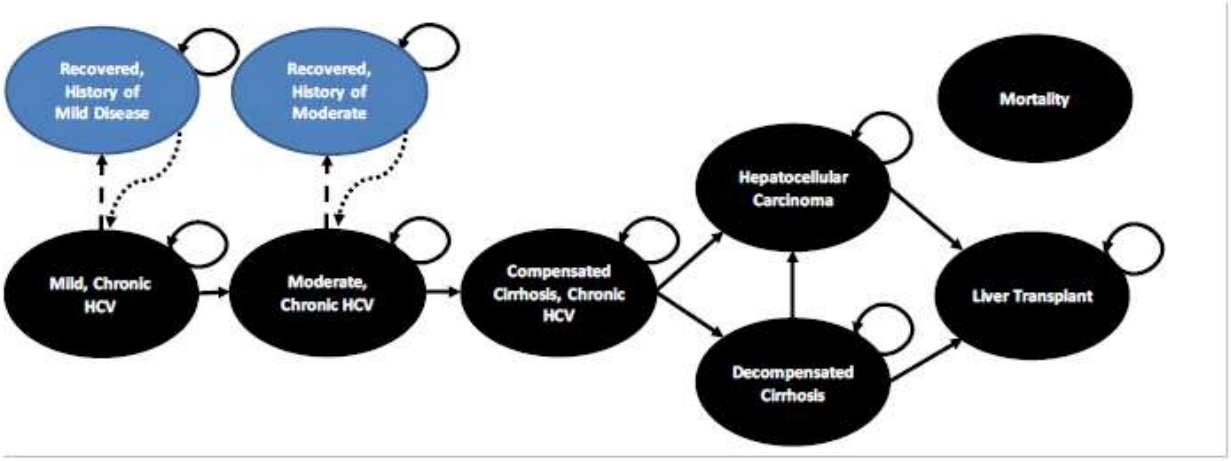
Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The natural history for hepatitis C virus (HCV) is modelled by the manufacturer using the structure in Figure 1.

FIGURE 1: NATURAL HISTORY SCHEMATIC (FIGURE 1 IN MANUFACTURER'S SUBMISSION)



Note: Health states are depicted by ellipses, while arrows represent permissible transitions between health states. Hashed arrows depict the possibility of achieving sustained virologic response (SVR). Dotted arrows depict a potential reinfection. Death is possible from any health state. Liver death is possible from decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant.

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

A discussion of the model structure is provided in the main body of the CADTH Common Drug Review (CDR) Pharmacoeconomic Review Report text. Treatments are incorporated into this natural history by modifying the costs and utilities of the nine states listed above, and by modifying the transition probabilities within this account. In this way, the changes to the model induced by treatment seek to account for how treatment modifies the natural history of the disease.

The manufacturer's submission considers three comparators (sofosbuvir plus ledipasvir [SOF/LDV], SOF plus pegylated interferon plus ribavirin [PR] [SOF + PR], PR alone) alongside the intervention of ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/RTV + RBV). Importantly, the manufacturer's submission does not include a watchful-waiting and/or no-treatment comparator, even though this is the current treatment strategy for many patients due to the burden of interferon-based treatment regimens. In contrast, the Excel model provided appears to allow for this functionality as long as some very simple functionality (e.g., insertion of results) is restored. The lack of a no-treatment option also makes the interpretation of results difficult.

In the case of treatment-naive patients, this is unlikely to be too much of an issue, since PR provides a cheaper, non-dominated alternative, and the only question would be whether the addition of no

treatment would result in PR being subject to extended dominance. Although this seems unlikely in the base case, it may be important within sensitivity analyses.

For treatment-experienced patients, however, the comparison of OBV/PTV/RTV + RBV with SOF/LDV means that only two relatively expensive treatments are compared. In this case, a no-treatment option may represent a cost-effective alternative that is not considered within the manufacturer's submission. This is particularly important, given that options providing for PR-containing regimens are not included in the model.

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Trial data are used for OBV/PTV/RTV + RBV.[6] Comparator data from an open-label study[7] and clinical trials.[8,9]	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	Structure based on Brady et al. (2007).[4] To convert the results in Thein et al. (2008)[5] to transition probabilities in the manufacturer's framework, the manufacturer used the Solver function in Excel to calibrate the probabilities so that the population would have a 16% prevalence of cirrhosis at 20 years.	
Utilities	Health Utilities Index Mark 3 data from Brady et al. (2007) for the model states.[4] Short-term "on-treatment" disutilities included based on trial data.[6,10,11]	The "trial data" for SOF/LDV do not relate to an SOF/LDV arm but instead to OBV/PTV/RTV + RBV. On-treatment disutilities are negative (health improving) in some cases, which appears unlikely.
Resource Use	Treatment duration is based on published trial data, with the method used to impute duration stated.	
Adverse Events	Active arms of three trials[6,7,9,18] for therapies evaluated and one NICE submission.	Adverse event data for SOF + PR and PR were not specific to genotype 4.
Costs		
• Drug	Wholesale price Delta PA database	
• AEs • Anemia • Depression • Rash • Neutropenia • Thrombocytopenia	Costs for anemia, rash and depression were based on Lachaine et al. (2014).[12] Costs for neutropenia and thrombocytopenia based on a single medical assessment using Ontario Ministry figures.[13]	

Data Input	Description of Data Source	Comment
Health state	Most health state costs based on Brady et al. (2007).[4] Costs in SVR stated to follow Liu et al. (2012) in assuming 50% of non-SVR states.[19]	Liu et al. (2012) not found in reference list.[19]

AE = adverse event; LDV = ledipasvir; NICE = National Institute for Health and Care Excellence; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
"No treatment" is not considered as a valid option for the economic model.	Considered under model structure, as above. Possibility of bias in model results in favour of OBV/PTV/RTV + RBV.
Efficacy (SVR) rates are identical across mild and moderate fibrosis stages.	This assumption may not be accurate. The manufacturer's sensitivity analyses suggest this may not have a major impact if the assumption does not hold.
Each year in SVR provides the same incremental utility vs. the non-SVR equivalent state.	This is justified using Brady et al. (2007) but is only a sensitivity analysis.[4] Brady instead assumes the increment applies for a single year.
On-treatment disutilities are provided for each treatment.	Some of these disutilities are negative, so that being on-treatment is argued to increase utility. The impact of this assumption is likely to be small but is likely to favour SOF/LDV over OBV/PTV/RTV + RBV and is likely to favour both treatments over regimens containing PR.
Adverse events in the model were anemia, rash, depression, neutropenia, and thrombocytopenia.	Trial data are used to suggest that these are relevant side effects.
Assumption made that AEs for comparators that are not reported do not occur in the model.	The lack of any liver-related side effects is concerning in light of the recent Health Canada and FDA warnings and may bias findings.

AE = adverse event; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; vs. = versus.

Manufacturer's Results

As only two groups are considered in the manufacturer's submission, a full discussion is provided in the main text. The tables summarizing the manufacturer's base case are reproduced here in Table 2 and Table 3.

It is worth noting that these tables refer to the deterministic results, rather than the (averaged) results of the probabilistic sensitivity analysis. Within the manufacturer's sensitivity analysis, only 500 iterations were used, which is not typically sufficient to provide reassurance that the full range of uncertainty will be captured.

The manufacturer's submission miscalculates the probability of each option being cost-effective in the head-to-head comparison ("Calc – Outputs [PSA]" in the Excel spreadsheet) and incorrectly specifies the cost-effectiveness frontier in both the submission document and the spreadsheet. In the former case, the calculations treat all negative incremental cost-effectiveness ratios (ICERs) as being cost-effective (as

opposed to being potentially dominated), and in the latter, the cost-effectiveness frontier is said to identify the option that is most likely to be cost-effective, as opposed to the option that is most cost-effective on the basis of expected costs and benefits.

CADTH Common Drug Review Analyses

For the treatment-naive cohort, the original analysis was replicated with two CDR modifications to the manufacturer's model. CDR notes that the economic model provided includes functionality to incorporate a no-treatment option with minor modifications. In practice, it is expected that one or more options will be cost-effective at a willingness-to-pay of $50,000 per QALY and that the no-treatment option is unlikely to be used. However, the exclusion of this no-treatment option may increase the circumstances under which the OBV/PTV/RTV regimen appears cost-effective, since having a no-treatment option allows the identification of cases in which extended dominance occurs, and here the relevant comparator is "no treatment" rather than an ineffective (dominated) alternative.

The model was also modified to use a larger number of model iterations within the calculation of probabilistic results. Within the modified base case (and other reanalyses), a total of 10,000 model iterations were used rather than the 500 in the manufacturer's model.

For the treatment-naive and treatment-experienced cohorts, the baseline results were rerun under this model. For each cohort, six additional analyses were conducted:

1. Two analyses that vary the utility increment following sustained virologic response (SVR):
    a. Lower SVR increment in each year in SVR
    b. The SVR increment applies to only the first year in SVR.

2. One analysis that varies the reinfection rate:
    a. 2% yearly reinfection rate, as opposed to the 1% used in the model.

3. Three analyses that vary the manufacturer's price:
    a. Price reduction of 20%
    b. Price reduction of 40%
    c. Price reduction of 60%

Treatment-Naive Cohort

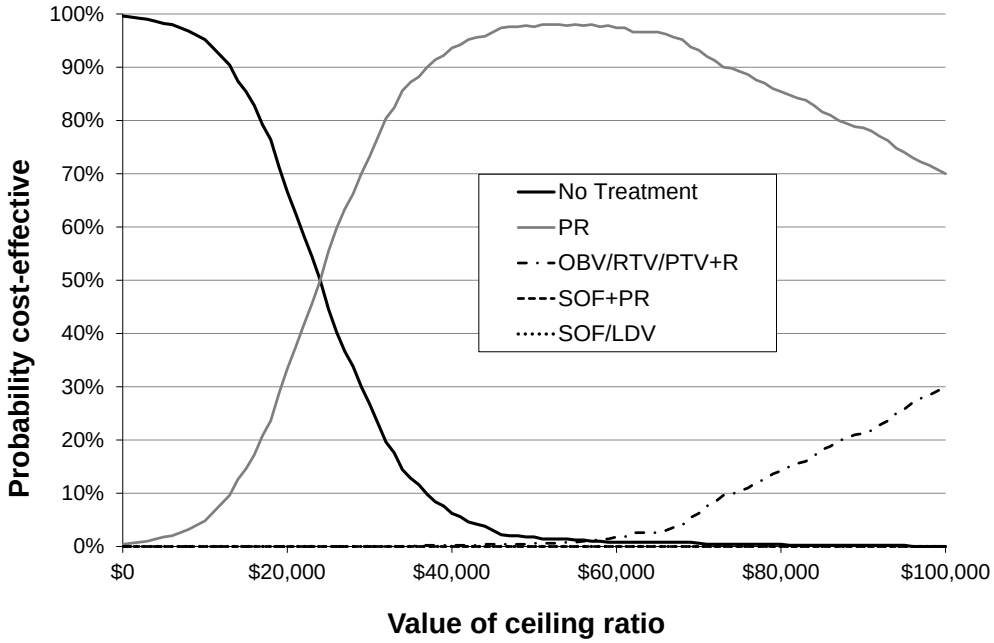
For the treatment-naive cohort, the revised base-case results appear as below. The main results from the manufacturer's base case are retained, with PR appearing as the most relevant comparator to OBV/PTV/RTV + RBV when assessing cost-effectiveness. In both the manufacturer's base case and the replication below, the incremental cost-utility ratio (ICUR) is around $113,000 per QALY and both SOF-containing regimens are dominated by the OBV/PTV/RTV + RBV treatment in cost-effectiveness terms. At a willingness-to-pay of around $50,000 per QALY, PR is both the most cost-effective option and the option most likely to be cost-effective (97.6%). For the remaining options, there is a 1.8% likelihood that the no-treatment option would be cost-effective and only a 0.6% likelihood that OBV/PTV/RTV + RBV is cost-effective.

TABLE 11: RERUN BASE CASE FOR TREATMENT-NAIVE PATIENTS

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$11,883		11.31		
PR	No treatment	$25,841	$13,958	11.94	0.63	$22,251
OBV/PTV/RTV + RBV	PR	$59,492	$33,651	12.24	0.30	$112,909
SOF + PR	OBV/PTV/RTV + RBV	$65,326	$5,834	12.20	–0.04	Dominated
SOF/LDV	OBV/PTV/RTV + RBV	$70,795	$11,302	12.20	–0.04	Dominated

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.

FIGURE 2: COST-EFFECTIVENESS ACCEPTABILITY CURVES — TREATMENT-NAIVE CDR BASE CASE



CDR = CADTH Common Drug Review; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; R = ribavirin; RTV = ritonavir; SOF = sofosbuvir.
Source: Generated from manufacturer's economic model.[3]

Modifying the utility increment for sustained virologic response

In the manufacturer's model, there are several sensitivity analyses that modify the assumptions surrounding quality of life. Most of these assumptions increase the likely cost-effectiveness of treatment. A key parameter in the model is the (fixed) 0.04 increment in quality of life assumed to occur in every year in which SVR has occurred. The CDR reanalyses consider two cases in which this parameter is modified. In the first, a lower (halved) yearly increment is considered. Here, an increment of 0.02 applied to every year in SVR was used in place of the manufacturer's assumption of an increment of 0.04 applying to every year in SVR.

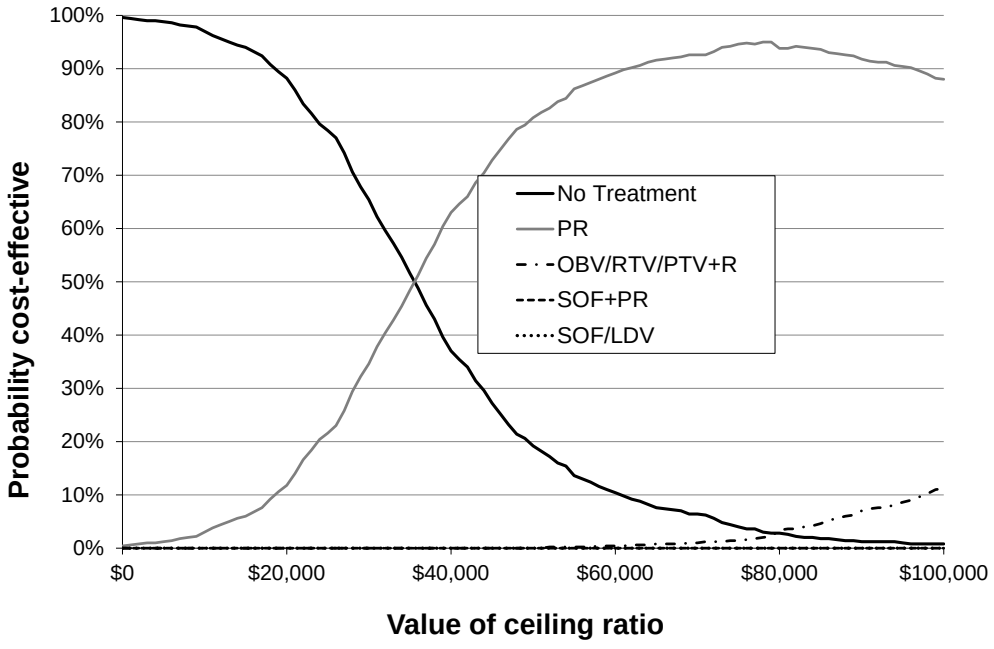
When this modified SVR assumption is used, the cost-effectiveness of PR and OBV/PTV/RTV + RBV both fall when considered against the no-treatment option. While the PR option remains the most cost-effective option at $50,000 per QALY, the ICUR for this PR versus no treatment has increased to $34,500 per QALY. For OBV/PTV/RTV + RBV, the ICUR versus PR increases by around 25%, to $141,000 per QALY. At a willingness-to-pay of $50,000 per QALY, PR has an 81% chance of being cost-effective, with the no-treatment option taking the remaining 19%. In none of the 10,000 model iterations did OBV/PTV/RTV + RBV appear cost-effective in this case.

TABLE 12: TREATMENT-NAIVE PATIENTS — LOWER YEARLY UTILITY INCREMENT

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$11,899		11.31		
PR	No treatment	$25,833	$13,934	11.71	0.40	$34,500
OBV/PTV/RTV + RBV	PR	$59,489	$33,656	11.95	0.24	$141,043
SOF + PR	OBV/PTV/RTV + RBV	$65,334	$5,845	11.92	–0.04	Dominated
SOF/LDV	OBV/PTV/RTV + RBV	$70,790	$11,300	11.92	–0.03	Dominated

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.

FIGURE 3: COST-EFFECTIVENESS ACCEPTABILITY CURVES — TREATMENT-NAIVE, LOWER SVR INCREMENT



LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; R = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response.
Source: Generated from manufacturer's economic model.[3]

While the manufacturer cites Brady et al.[4] as the basis for the approach taken, the yearly 0.04 SVR increment was not the base case in Brady et al. but was instead a sensitivity analysis only. In the Brady et al. base case, the utility increment was applied only in the first year of SVR. As a half-cycle correction was used, the CDR modified the utility figures that applied in the first and second periods of the model.

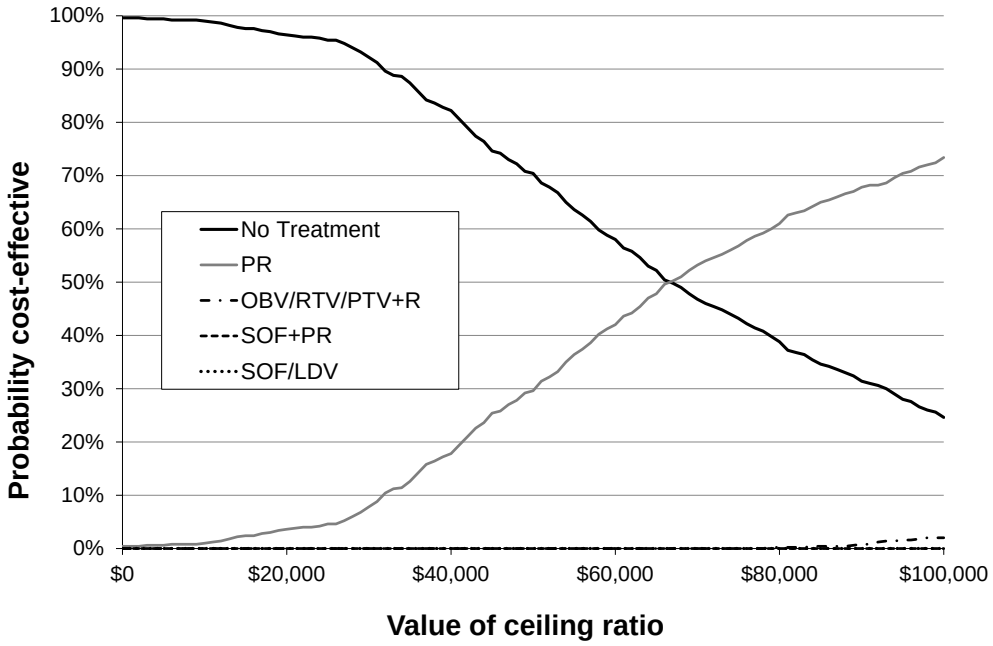
In this case, the impact of the alternative assumption is greater than in the previous case. Here, the incremental QALY gain for OBV/PTV/RTV + RBV against PR falls to around 62% of its base-case value. (Note that some of the QALY gain is due to decreased progression and increased survival, and this gain is not sensitive to the SVR assumption.) Here, the cost per QALY rises to around $180,000 per QALY. In this case, the PR regiment is no longer the most efficient option at $50,000 per QALY, with the no-treatment option instead being cost-effective. In this case, PR is cost-effective in around 30% of model iterations, with no treatment being cost-effective in all others.

TABLE 13: TREATMENT-NAIVE PATIENTS — UTILITY INCREMENT TO FIRST YEAR IN SVR ONLY

	Comparator	Total Costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$11,833		11.32		
PR	No treatment	$25,786	$13,953	11.53	0.21	$65,870
OBV/PTV/RTV + RBV	PR	$59,449	$33,663	11.72	0.19	$180,362
SOF + PR	OBV/PTV/RTV + RBV	$65,316	$5,868	11.68	–0.04	Dominated
SOF/LDV	OBV/PTV/RTV + RBV	$70,752	$11,303	11.70	–0.02	Dominated

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; vs. = versus.

FIGURE 4: COST-EFFECTIVENESS ACCEPTABILITY CURVES — TREATMENT-NAIVE, SINGLE-YEAR SVR INCREMENT



LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; R = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response.
Source: Generated from manufacturer's economic model.[3]

Modifying the reinfection rate

Increasing the reinfection rate from 1% to 2% did not seem to significantly impact results, with the ICUR increasing from $112,909 per QALY (base case) to $120,579 (2% reinfection rate).

Price reduction for OBV/PTV/RTV + RBV

Given the relatively low likelihood of cost-effectiveness for OBV/PTV/RTV + RBV in treatment-naive patients, scenarios were considered for price reductions of 20%, 40%, and 60% from the manufacturer's suggested price. For the first two reductions, the main comparison for cost-effectiveness of OBV/PTV/RTV + RBV is against PR, with the ICUR above $50,000 per QALY for the 20% price reduction and below this figure for the 40% price reduction. For the 60% price reduction, PR would be eliminated when considering the cost-effective option by extended dominance. Here, versus no treatment, OBV/PTV/RTV + RBV has an ICUR around $15,000 per QALY.

The incremental cost for OBV/PTV/RTV + RBV versus PR falls in an approximately linear way, with about a $5,600 fall for every 10% price reduction. This allows a calculation of the price reduction necessary to achieve a $50,000 per QALY ICUR. Here, for a price reduction of around 34%, an ICUR of approximately $49,000 per QALY would be expected.

TABLE 14: TREATMENT-NAIVE, OBV/PTV/RTV + RBV PRICE REDUCTIONS

Reduction	Comparator	Incremental Cost vs. Comparator ($)	Incremental QALYs vs. Comparator	ICUR (per QALY)
0%	PR	$33,651	0.30	$112,909
20%	PR	$22,474	0.30	$74,932
34%[a]	*PR*	*$14,672*	*0.30*	*$49,176*
40%	PR	$11,323	0.30	$37,992
60%	No treatment	$14,053	0.93	$15,157

ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.
[a] Estimated using linear fall in incremental costs.

Treatment-Experienced Cohort

For the treatment-experienced cohort, no data were provided for the two PR-based regimens (SOF + PR, and PR). In the manufacturer's analysis, this leaves a comparison between OBV/PTV/RTV + RBV and SOF + LDV only. Even with the addition of a no-treatment option, this leaves only a small number of possible comparators within the model.

Within the manufacturer's submission, OBV/PTV/RTV + RBV is considered alongside SOF/LDV. In this case, treatment with OBV/PTV/RTV + RBV is suggested to be around $12,400 cheaper per patient in the deterministic analysis. In addition, OBV/PTV/RTV + RBV is also argued to provide approximately 0.13 additional QALYs and is therefore argued to dominate SOF/LDV.

In the CDR reanalysis using a no-treatment option and 10,000 model iterations, very similar figures are obtained for both incremental costs ($12,393, 0.13 additional QALYs). However, the possible consideration of no treatment is potentially important, as the ICUR for OBV/PTV/RTV + RBV versus no treatment is around $52,000 per QALY.

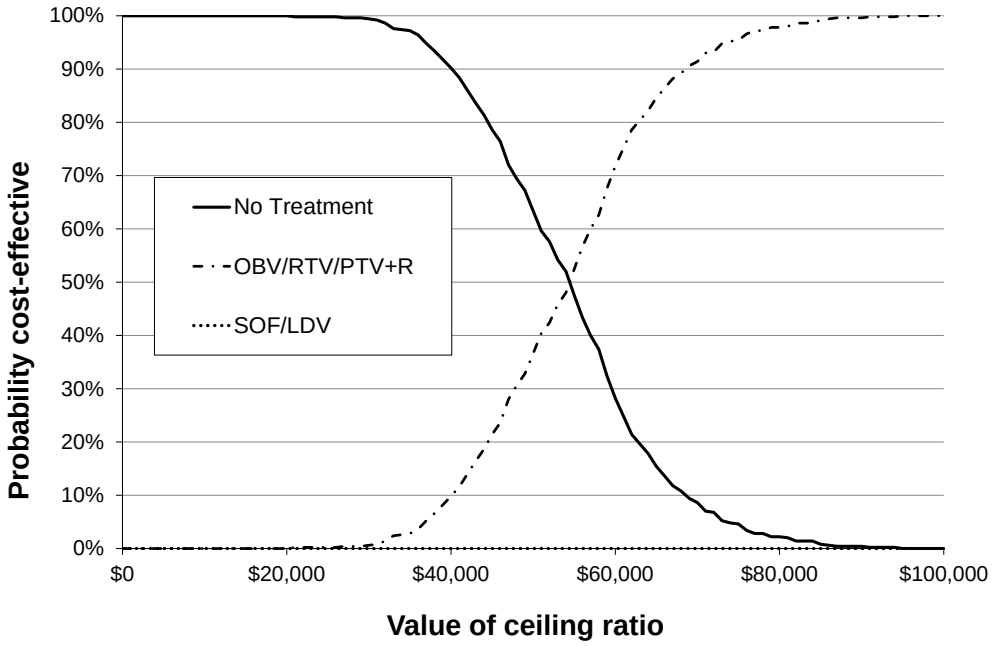
TABLE 15: TREATMENT-EXPERIENCED, CADTH COMMON DRUG REVIEW BASE CASE

	Comparator	Total costs ($)	Incremental Cost vs. Comparator ($)	Total QALYs	Incremental QALYs vs. Comparator	ICUR (per QALY)
No treatment	(Baseline)	$12,276		10.59		
OBV/PTV/RTV + RBV	No treatment	$59,422	$47,147	11.49	0.90	$52,346
SOF/LDV	OBV/PTV/RTV + RBV	$71,816	$12,393	11.36	–0.13	Dominated

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; vs. = versus.

In this case, at $50,000 per QALY, OBV/PTV/RTV + RBV has about a 37% likelihood of being a cost-effective option versus no treatment (63%).

FIGURE 5: COST-EFFECTIVENESS ACCEPTABILITY CURVES — TREATMENT-EXPERIENCED CDR BASE CASE



CDR = CADTH Common Drug Review; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RTV = ritonavir; SOF = sofosbuvir.
Source: Generated from manufacturer's economic model.[3]

Modifying the utility increment for sustained virologic response

In the cases where the utility benefits from achieving SVR are again reduced, the ICURs increase from around $52,346 to $74,518 (halved utility benefit from SVR) and $116,633 (utility benefit applies in first SVR-year only). The corresponding likelihood of cost-effectiveness (at $50,000 per QALY) is likewise affected, with this equal to 37% in the modified base case but only 3.8% and 0.4% in the two alternative cases.

TABLE 16: TREATMENT-EXPERIENCED ICURS FOR OBV/PTV/RTV + RBV, VARYING SVR ASSUMPTIONS

Assumption	Comparator	Incremental Cost vs. Comparator ($)	Incremental QALYs vs. comparator	ICUR (per QALY)
Baseline (0.04 per SVR-year)	No treatment	$47,147	0.90	$52,346
0.02 per SVR-year	No treatment	$47,064	0.63	$74,518
0.04 in first SVR-year	No treatment	$47,089	0.40	$116,633

ICUR = incremental cost-utility ratio; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; SVR = sustained virologic response; vs. = versus.

It should be noted that in all three of these cases, OBV/PTV/RTV + RBV continues to dominate SOF/LDV, as suggested in the manufacturer's submission.

Modifying the reinfection rate

As in the treatment-naive case, increasing the reinfection rate from 1% to 2% did not seem to significantly affect results, with the ICUR increasing from $52,346 per QALY (base case) to $58,350 (2% reinfection rate).

Price reduction for OBV/PTV/RTV + RBV

The scenarios considering price reductions for OBV/PTV/RTV + RBV again improve the cost-effectiveness of this treatment versus the nearest comparator, in each case no treatment. For even a very small price reduction, the OBV/PTV/RTV + RBV treatment is likely to be cost-effective at $50,000 per QALY. Again, the fact that the incremental costs fall consistently with each percentage discount can be used to estimate the price reduction necessary to reach $50,000 per QALY. In this case, a reduction of 4% appears to be sufficient.

TABLE 17: TREATMENT-EXPERIENCED, OBV/PTV/RTV + RBV PRICE REDUCTIONS

Reduction	Comparator	Incremental Cost vs. Comparator ($)	Incremental QALYs vs. Comparator	ICUR (per QALY)
0%	No Treatment	$47,147	0.90	$52,346
4%[a]	No Treatment	$44,914	0.90	$49,868
20%	No Treatment	$35,959	0.90	$39,333
40%	No Treatment	$24,808	0.90	$27,590
60%	No Treatment	$13,655	0.90	$15,183

ICUR = incremental cost-utility ratio; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life-year; RBV = ribavirin; RTV = ritonavir; vs. = versus.

[a] Estimated using linear fall in incremental costs.

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