Common Drug Review
Pharmacoeconomic Review Report

May 2016

Drug	Elbasvir/Grazoprevir (Zepatier)
Indication	For the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults as follows: Without ribavirin: • in genotype (GT) 1 or 4 treatment-naive (TN) and peginterferon alfa + ribavirin (PR) treatment-experienced (TE) relapsers (12 weeks) • in GT1 protease inhibitor (PI)/PR-TE relapsers (12 weeks) • in GT1b TN, non-cirrhotic patients (8 weeks) • in GT1b PR- or PI/PR-TE on-treatment virologic failures (12 weeks) With ribavirin: • in GT1a PR- or PI/PR-TE on-treatment virologic failures (16 weeks) • in GT4 PR-TE on-treatment virologic failures (16 weeks) With sofosbuvir: • in GT3 TN patients (12 weeks)
Reimbursement request	As per indication
Dosage form(s)	Elbasvir/Grazoprevir in a single tablet (50/100 mg) for oral administration
NOC date	19 January 2016
Manufacturer	Merck Canada Inc.

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

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
CHC	chronic hepatitis C
CI	confidence interval
DAS	dasabuvir
EBR	elbasvir
GT	genotype
GZR	grazoprevir
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
LED	ledipasvir
OMB	ombitasvir
PAR	paritaprevir
PEG	pegylated interferon
PR	pegylated interferon plus ribavirin
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RBV	ribavirin
RIT	ritonavir
SMV	simeprevir
SOF	sofosbuvir
SVR	sustained virologic responses
TE	treatment-experienced
TN	treatment-naive

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	EBR/GZR (Zepatier)
Study Question	What is the cost-effectiveness of treatments with EBR/GZR regimens compared with various standards of care regiments for the treatment of HCV GT 1, 3, 4 infections in TN and TE patients?
Type of Economic Evaluation	Cost-utility analysis
Target Population	• TN patients in GT 1, 3, 4 • TE relapsers in GT 1, 4 • TE failures (non-relapsers) in GT 1, 4
Treatment	TN and TE relapsers in GT 1, 4: EBR/GZR for 12 weeks TN GT 3: EBR/GZR plus SOF for 12 weeks TE failures in GT 1b: EBR/GZR for 12 weeks TE failures in GT 1a, 4: EBR/GZR plus RBV for 16 weeks
Outcomes	• SVR • QALYs
Comparators	GT 1: No Treatment, PR, LDV + SOF, Holkira Pak (OMB/PAR/RIT+DAS ± RBV), SIM + PR, SIM + SOF, SOF + PR. GT3: No Treatment, PR, SOF + RBV GT4: No Treatment, PR, SOF + PR
Perspective	Payer perspective (provincial Ministry of Health)
Time Horizon	Lifetime horizon (to 110 years of age)
Results for Base Case	• EBR/GZR is cost-effective versus all comparators at < $50,000 per QALY in GT 1 and 4. • EBR/GZR is not cost-effective at $50,000 per QALY versus PR in GT 3.
Key Limitations	• Manufacturer's submitted model lacks detail in places and required reconstruction by CDR.
CDR Estimates	**GT 1:** • ICUR for EBR/GZR vs. PR or No Treatment ranges from $4,000 to $18,000 per QALY. **GT 3:** • ICUR for EBR/GZR vs. PR is $115,659 per QALY (non-cirrhotic subgroup) or $75,309 (cirrhotic). • EBR/GZR is not cost-effective at $50,000 per QALY when compared with PR. **GT 4:** • ICUR for EBR/GZR vs. PR or No Treatment ranges from $6,000 to $28,000 per QALY.

CDR = CADTH Common Drug Review; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HCV = hepatitis C; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive.

EXECUTIVE SUMMARY

Background

Elbasvir/grazoprevir (EBR/GZR; Zepatier) is a fixed dose combination of two antiviral agents indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, and 4 infections in adults.[1] The recommended dose contains 50 mg elbasvir and 100 mg grazoprevir, and is taken once daily. At the confidential submitted price ([redacted] per 100/50 tablet), a standard 12-week course of treatment would cost [redacted].[2]

Table 2 provides a list of the regimens suggested in the manufacturer's main analysis. The manufacturer also provides for the possibility that treatment duration might be reduced to eight weeks for treatment-naive, genotype 1b patients without significant fibrosis or cirrhosis ([redacted] per patient-course).

TABLE 2: TREATMENT REGIMENS OF DCV+SOF AND DURATION BY PATIENT POPULATION WITHIN MAIN ANALYSES

Patient Population	Regimen	Duration (Weeks)
GT 1 TN	EBR/GZR	12
GT1 TE (relapse)	EBR/GZR	12
GT 1a TE (other virologic failures)	EBR/GZR + RBV	16
GT 1b TE (failure)	EBR/GZR	12
GT 3 TN	EBR/GZR + SOF	12
GT 4 TN	EBR/GZR	12
GT 4 TE (relapse)	EBR/GZR	12
GT4 TE (other virologic failures)	EBR/GZR + RBV	16

DCV = daclatasvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.
Source: Adapted from the Manufacturer's pharmacoeconomic submission.[3]

The manufacturer submitted a cost-utility analysis over a lifetime horizon (to 110 years of age) from a provincial Ministry of Health perspective.[3] The analysis assesses the cost-effectiveness of EBR/GZR for treatment-naive and treatment-experienced subgroups, as well as patients with and without cirrhosis. The comparators varied by genotypes and consisted of new direct-acting antiviral agents (DAAs), pegylated interferon plus ribavirin (PR), and a no-treatment option. The submission uses a Markov model that tracks the natural history of the disease, and incorporates the treatment by allowing for sustained virologic response (SVR) states in which disease progression is halted.

The manufacturer suggests that EBR/GZR is cost-effective at $50,000 per quality-adjusted life-year (QALY) in genotype 1 and genotype 4 patients but is not cost-effective for treatment-naive genotype 3 patients.

The manufacturer's model appears to have used an appropriate mix of comparators, including both a No-Treatment option, a PR option and, where possible, contemporary direct-acting agents. This provides more context to the model results than would be obtained were these items missing.

Summary of Identified Limitations and Key Results

The main limitation of the manufacturer's pharmacoeconomic submission relates to a lack of justification and detail as to its selected approach in modelling and an unnecessarily complex Excel model spreadsheet. The lack of transparency complicated the review and assessment of the manufacturer's approach. The CADTH Common Drug Review (CDR) determined few differences to the results when accounting for changes in parameters and/or uncertainty. As such, the model is robust to key aspects identified.

As a broader issue for consideration, approval by the US FDA for EBR/GZR for genotypes 1 and 4 recommends pre-testing prior to regimen selection and treatment duration. This approach, if taken in Canada, could affect the cost-effectiveness of EBR/GZR.

Conclusions

The manufacturer's submission considered the cost-effectiveness of EBR/GZR in treatment-naive and treatment-experienced patients across genotypes (1/1a/1b, 3, and 4) and cirrhosis status (cirrhotic disease, non-cirrhotic disease). Overall, the comparative evidence of clinical effectiveness suggests that EBR/GZR is cost-effective for patients with CHC who are genotype 1 and genotype 4, irrespective of cirrhosis status and prior exposure.

In genotype 3, EBR/GZR does not appear to be cost-effective at the submitted price. In this case, the comparators considered are No Treatment, PR, and sofosbuvir plus ribavirin (SOF + RBV). PR appears highly cost-effective versus No Treatment. When compared with PR, the incremental cost-utility ratio (ICUR) for EBR/GZR exceeds $60,000 per QALY. Based on CDR reanalyses, a price reduction of 44% for EBR/GZR would be required for the treatment of patients without cirrhosis and a 36% price reduction for patients with cirrhosis.

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 17 distinct health states.[3] The manufacturer claims that this is based on a model developed, validated, and published by Merck.[4-6] The submitted model considers hepatitis C virus (HCV) genotypes 1, 3, 4 and 6, but only genotypes 1, 3 and 4 were included in the review.

The schematic for this natural history model is provided in Figure 1, Appendix V. All patients are assumed to begin in one of these five states, defined using the METAVIR classification: including no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with multiple septa (F3), and compensated cirrhosis (F4). Five states allow for a sustained virologic response (SVR) from each of the METAVIR states, as SVR F0 to F4. Where SVR is achieved, the model also allows for fibrosis regression from the compensated cirrhosis (SVR F4) to portal fibrosis with multiple septa (SVR F3).

Disease progression from the two states with compensated cirrhosis (F4, SVR F4) leads to either decompensated cirrhosis and hepatocellular carcinoma (in each case, allowing separate states for first and subsequent years). Progression is also possible from decompensated cirrhosis to hepatocellular carcinoma, and from both sets of states to liver transplantation (again, allowing separate states for first and subsequent years). The final two states distinguish between death from liver-related and other-causes. Liver-related deaths are defined as excess mortality applying in decompensating cirrhosis, hepatocellular carcinoma, and liver transplantation 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 health states. By assigning quality of life to each state, quality-adjusted life-years (QALYs) can be derived and the main outcome of the analysis is cost-utility, in terms of incremental cost-utility ratios (ICURs). The perspective of the model was from a provincial Ministry of Health, including drug acquisition costs, medical costs related to chronic hepatitis C (CHC) and complications, costs associated with treatment-related adverse events (anemia, depression, rash).

The manufacturer's economic model allows for reinfection, although there are some potential issues with the way that this is implemented within the model (see Limitations). Patients who do re-enter the HCV states at F0 or F4 are not re-treated.

The structure of the manufacturer's model allows outcomes to be considered for a cohort of patients of a given gender and age. Unless these factors affect results in an additional way, gender and age tend to have an impact on results as they affect the relevant mortality applying within the model to the selected cohort. As a result, it is common for models to use a mean age and/or average life table results across genders for parsimony.[7] The manufacturer's model takes a complex approach and runs the model assuming the midpoint of six age bands (20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥ 70) and dichotomous gender (male/female), so that the model is run separately 12 times and then combined. A large number of individual models are combined to provide the results quoted by the manufacturers, based on both 12 demographic subgroups and 154 scenarios considered, leading to 1,848 separate

model runs. There appear to be issues in the way that individual model results have been computed prior to their being combined together, which risks underestimating uncertainty in outcomes for both treatments and comparators (see Limitations).

The treatments considered in the model use EBR/GZR for eight, 12, or 16 weeks depending on genotype (1, 3, 4) as well as treatment history and response status (treatment-naive or treatment-experienced relapsers or treatment-experienced failures). For the treatment-experienced failures, ribavirin is added to EBR/GZR, and for treatment-naive genotype 3 patients, sofosbuvir (SOF) is added to EBR/GZR. A range of comparators are considered in the model, depending on the genotype and prior treatment or response status; with each model considering no treatment; pegylated interferon plus ribavirin (PR); and one or more SOF-containing regimens. For genotype 1, three SOF-containing regimens were considered alongside Holkira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin) and simeprevir (SIM) + PR.

Clinical effectiveness is assessed using SVR data. For the treatment regimens, SVRs were stated to be based on registration studies, where the treatment arms are the same as those used in the model. The estimates for mean efficacy (based on SVR at 12 weeks) ranged from 86.4% (for genotype 1a, treatment failures) to 100% (multiple subgroups). The manufacturer's submission sets out the specific assumptions used (Tables 7 to 10 in the manufacturer's submission) but while the trials contributing toward these estimates are identified in Appendix A-1, it is not clear which of the trials has specifically informed the estimates used and how precisely the figure is obtained. This raises issues of the consistency of approach across eligible trials.

For the comparator interventions, the efficacy estimates were stated to be based on a systematic review of randomized controlled trials (RCTs) where at least one arm assessed an intervention of interests, plus single-arm studies with an intervention of interests. SVR rates across these cases range from 16.9% (PR for genotype 1a, treatment failures, cirrhotic) to 100% (multiple subgroups). As with the EBR/GZR case, the specific assumptions used are identified in the submission, but the sources of these assumptions are not clear from the data provided in the appendices (Appendix A-2).

Data for discontinuation rates for comparator interventions were taken from the CADTH Therapeutic Review report[7] and were applied across genotype and cirrhosis status. For EBR/GZR, discontinuation rates were taken from trial data and allowed to vary within genotype. The base-case values for these figures are below 10%, except for PR (17% treatment-naive, 11% treatment-experienced) and SOF+PR (11% treatment-naive). Similarly, adverse event data were taken from these same sources, with depression, anemia, and rash considered.

Quality of life data for the fibrosis states (with and without SVR) are based on Health Utilities Index Mark 2 (HUI-2) data from Hsu et al.[8] The increase in utility from SVR is 0.02 for SVR F0 to F3 versus F0 to F3, and 0.07 for SVR F4 versus F4. All utilities were adjusted proportionally to reflect age-based norms for Canadian HUI-3 utilities,[9] although it is unclear how these were obtained from the information published in the source provided.[10] It was stated that utilities for decompensated cirrhosis were based on McLernon et al.,[11] but the figure used for decompensated cirrhosis (0.65) appears to differ from the estimated EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) utility provided by that systematic review (0.79). The utility for post–liver transplantation (0.75) appears to be a HUI-2 based.[8] An on-treatment disutility of 0.11 was assigned for treatments including pegylated interferon or RBV.[12] On-treatment disutility for all other treatments assumes no difference from baseline utility (F0 to F3). No trial data appear to have been presented for health utilities for those receiving EBR/GZR.

Health state costs are based primarily on Myers et al.,[13] with adverse events costs from the CADTH Therapeutic Review report.[7] Drug costs are based on manufacturer list prices, with all non-2015 costs inflated to 2015 using health care component of the Statistics Canada Consumer Price Index (August 2015).[14]

2. MANUFACTURER'S BASE CASE

The manufacturer's submission provides a series of analyses in subgroups differentiated by disease genotype (1, 3, 4), prior exposure to treatment (Treatment-Naive, Treatment-Experienced) and cirrhosis (cirrhotic, non-cirrhotic). Given the number of distinct pieces of information provided, a summary of the information is provided below, with a more complete version appearing in the Appendix of this report.

For genotype 1, the manufacturer considers EBR/GZR alongside both No Treatment and six other active treatments (PR, SIM+PR, SOF+PR, OMB/PAR/RIT+DAS ± RBV, SIM+SOF and LDV/SOF). The EBR/GZR-containing regimens are suggested to be the most cost-effective option at a relatively low cost per QALY, with this ICUR ranging from $4,778 per QALY to $17,834. In three of the four cases (not displayed), a comparator regimen (either LDV/SOF or OMB/PAR/RIT+DAS±RBV) is more effective but is sufficiently more costly, such that EBR/GZR appears cost-effective. The only case (Table 3) in which there is any question of cost-effectiveness is the Treatment-Experienced, Non-Cirrhotic case in which OMB/PAR/RIT+DAS± RBV becomes cost-effective at ~$80,000 per QALY.

TABLE 3: SELECTED MANUFACTURER'S RESULTS FOR EBR/GZR PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs) — Sequential
Genotype 1, treatment-experienced, non-cirrhotic					
No Treatment	17,020	9.49			
EBR/GZR ± RBV	53,557	11.54	36,537	2.05	17,834
OMB/PAR/RIT+DAS± RBV	60,068	11.62	6,511	0.08	79,581
Genotype 3, treatment-naive, non-cirrhotic					
No Treatment	19,052	9.20			
PR	24,720	10.55	5,668	1.35	4,199
EBR/GZR	98,742	11.66	74,022	1.11	66,933
Genotype 3, treatment-naive, cirrhotic					
No Treatment	33,036	6.93			
PR	34,634	8.89	1,598	1.95	818
EBR/GZR	108,119	10.08	73,485	1.19	61,527
Genotype 4, treatment-naive, non-cirrhotic					
No Treatment	16,028	9.64			
PR	24,421	10.58	8,393	0.95	8,854
EBR/GZR	45,556	11.61	21,135	1.02	20,676
SOF+PR	63,241	11.69	17,685	0.08	208,971

EBR = elbasvir; DAS = dasabuvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; RIT = ritonavir; SOF = sofosbuvir.
Source: Adapted from the Manufacturer's pharmacoeconomic submission.[3]

For genotype 3, the manufacturer provides outcomes for treatment-naive cases. In both of these cases (Table 3), EBR/GZR is compared within the sequential analysis against PR and has an ICUR exceeding $50,000 per QALY. The manufacturer provides cost-effectiveness acceptability curves resulting from the

probabilistic sensitivity analysis, although these are not displayed because of concerns surrounding the generation of results.

Finally, for genotype 4, the manufacturer provides comparisons for treatment-naive and treatment-experienced cases. In three of the four cases (not displayed), EBR/GZR (with RBV in the Treatment-Experienced scenarios) is stated to be the most effective treatment and dominates the other two antiviral agents (PR and SOF+PR). In each of these cases, the ICUR of EBR/GZR versus No Treatment ranges from $4,514 to $18,106 per QALY. In the remaining case (Table 3), all four options considered appear cost-effective for at least some values of the cost-effectiveness threshold. However, EBR/GZR again provides an ICUR below $50,000 and while SOF+PR is more effective, its ICUR exceeds $200,000 per QALY.

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer's sensitivity analyses included additional "secondary" analyses conducted with the model in other subgroups, a large number of univariate sensitivity analyses varying each model parameter in turn and probabilistic sensitivity analyses.

The manufacturer presents one case for genotype 1b patients without significant fibrosis or cirrhosis (METAVIR stages F0 to F2), which was identified in the manufacturer's submission as a group in which an eight-week treatment duration may be appropriate. In this case, as in the genotype 1 case broadly, EBR/GZR appears cost-effective. As a broad result, the ICUR for the eight-week regimen (in a selected sample) was around $10,000 per QALY as compared with around $13,000 per QALY for the more standard 12-week regimen.

The univariate sensitivity analyses presented by the manufacturers suggest that the most cost-effective option is insensitive to the values of individual parameters. Treatment-experienced HCV monoinfected subjects with genotype 1a infection who had on-treatment virologic failures receive a 16-week course of treatment on EBR/GZR, as compared with the standard 12-week treatment. For genotype 1, the proportion of these patients will affect the cost-effectiveness of OMB/PAR/RIT+DAS ± RBV versus EBR/GZR. In the base case, this proportion is 41% and the ICUR is $79,581; where it increases to 52%, the ICUR falls to $37,340 per QALY.

For genotype 3, the relevant ICUR is between PR and EBR/GZR, where the base case suggests that PR is cost-effective at $50,000 per QALY. The only parameters able to reduce this ICUR below $50,000 were (1) a higher SVR for EBR/GZR from F4 (99.2%), (2) a lower regimen cost for EBR/GZR, and (3) a higher probability of hepatocellular carcinoma from compensated cirrhosis (F4) (7.9% per year).

For genotype 4, the univariate analyses do not display ICURs for the most relevant comparisons as far as judging cost-effectiveness is concerned.

Probabilistic sensitivity analyses are provided by the manufacturer, but due to the method used to generate their results, it seems unlikely that they can correctly characterize uncertainty in the results. Therefore, they are not presented.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The CADTH Common Drug Review (CDR) identified a number of limitations regarding the manufacturer's pharmacoeconomic submission, relating specifically to the submitted Excel model. In particular, the model provided was very complex, and the degree of complexity does not appear justified as it relates to the coding of the model, rather than the underlying decision problem. The model takes around 12 hours to run a single probabilistic sensitivity analysis involving only 1,000 iterations. CDR was able to replicate the model in the same structure to allow scenarios to be considered with a greater number of model iterations and flexibility over which elements of the model would be considered.

The methods used within the submitted model were of some concern; in particular, the submitted model appears to both restrict the use random numbers (by defining a random number seed so that the same "random" numbers are used every time the model runs) and the submitted model appears to obtain figures for costs and benefits independently of each other (rather than together, and linked to parameters that might be expected affect all items together).

The reporting of several elements of the manufacturer's methodology is incomplete, so that the justification of the approach is not fully transparent. This is most problematic in the reporting of utility figures; as such, alternative utility values were tested by CDR. This did not significantly affect results and is reported only briefly within the appendices.

The model also assumes that any reinfections following a person achieving SVR from F0 to F3 will result in the patient returning back to the METAVIR F0 state. This suggests that a patient with portal fibrosis with numerous septa without cirrhosis (F3) could achieve SVR in the following cycle (year) with the same fibrosis status (SVR F3) but on reinfection the fibrosis would automatically disappear (F0). This does not appear to be credible but is not expected to significantly affect the model results.

The models provided by the manufacturer do not distinguish between those patients who can easily tolerate specific drugs and those who do not. This is a particular issue for the ribavirin-containing regimens. In the manufacturer's model, those receiving these regimens receive a sizable reduction in their mean utility value, on the basis that many patients will shave issues with tolerability. This will also affect the likely effectiveness of treatment, given discontinuations. The manufacturer's model does not allow separate analyses to be run for those who are (1) "tolerant" and (2) "intolerant" to ribavirin-containing regimens. Had such models been provided by the manufacturer, it is possible that the results of some comparisons would have been affected; e.g., making EBR/GZR more cost-effective for "intolerant" patients but less cost-effective for "tolerant" patients.

3.1 CADTH Common Drug Review Reanalyses

Given the concerns relating to the manufacturer's model, CDR focused on replicating the manufacturer's approach and results in a validation exercise. Following clinical input, a single cohort was considered for the model in which 60% of patients are male and the average age of the cohort is 45 and the model, where possible, considered genotypes 1a and 1b separately.

For the treatment-naive analyses considering genotypes 1a and 1b (plus non-cirrhotic or cirrhotic), the results are broadly similar to the manufacturer's model for genotype 1 (combining both groups). Overall, the ICUR for EBR/GZR versus PR appears to be slightly lower than the corresponding ICUR that might be expected from the manufacturer's base case.

Within the treatment-experienced genotype 1 group, it was not possible to distinguish between genotypes 1a and 1b using the subgroups provided by the manufacturer. As a result, the broad genotype 1 is retained and the analyses provided broadly similar results. In the non-cirrhotic subgroup, the probabilistic sensitivity analysis suggests that an ICUR for EBR/GZR versus No Treatment of approximately $16,000, with OMB/PAR/RIT+DAS ± RBV becoming cost-effective once each QALY is valued above $60,000. At a willingness to pay of $50,000 per QALY, there is a 63% likelihood that EBR/GZR is cost-effective, with OMB/PAR/RIT+DAS ± RBV having the remaining 37% likelihood of cost-effectiveness.

For the treatment-naive genotype 3 groups, the manufacturer's analysis suggests that PR is more cost-effective at $50,000 per QALY. The ICUR for EBR/GZR versus PR is higher within the CDR analysis, at $115,659 per QALY (non-cirrhotic) and $75,309 per QALY (cirrhotic) using the manufacturer's confidential price ([redacted] per week). In order to obtain a cost per QALY of $50,000, a discount of 44% (i.e., to [redacted] per week) is required for the non-cirrhotic case. A discount of 26% (i.e., to [redacted] per week) is required to achieve the $50,000 per QALY mark for cirrhotic, treatment-naive genotype 3 patients. For ICURs from these and additional scenarios, see Table 4.

TABLE 4: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Submitted Drug Versus Comparator		
Price	**Genotype 3, Treatment-Naive, Non-cirrhotic**	**Genotype 3, Treatment-Naive, Cirrhotic**
CDR reconstructed	$115,659 per QALY	$75,309 per QALY
10% reduction	$100,580 per QALY	$65,795 per QALY
20% reduction	$85,420 per QALY	$55,747 per QALY
26% reduction	NA	$49,568 per QALY
30% reduction	$70,001 per QALY	$44,968 per QALY
40% reduction	$55,710 per QALY	$34,944 per QALY
44% reduction	$49,221 per QALY	NA
50% reduction	$40,542 per QALY	$25,189 per QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

Finally, for genotype 4, the manufacturer results suggested that EBR/GZR would be cost-effective at $50,000 per QALY regardless of prior treatment exposure and cirrhosis status. The same general results are obtained in the CDR reanalysis, with at least a 90% likelihood of cost-effectiveness for EBR/GZR in three of four cases. In the remaining case (treatment-experienced, non-cirrhotic), there is around a 74% likelihood of cost-effectiveness for EBR/GZR with the remaining 26% likelihood attached to SOF/RBV. While EBR/GZR appears cost-effective overall, there is significant uncertainty as to the most cost-effective option over a wide range of values for the cost-effectiveness threshold.

4. ISSUES FOR CONSIDERATION

- It has not been possible to distinguish between genotype 1a and genotype 1b treatment-experienced cohorts and it is not clear if clinically significant differences exist between them. While EBR/GZR in treatment-experienced patients with genotype 1 infection appears cost-effective, there may be differences between these subgroups that cannot be assessed with the available information.
- There appear to be significant differences in the recommended use of Zepatier within the US as compared with the use identified in the manufacturer's submission, especially for patients with genotypes 1a and 4. If the US recommendations are implemented "off-label" in Canada, then there is a potential that this will worsen the case for cost-effectiveness of EBR/GZR.

For genotype 1a patients:

- The US recommendations suggest that all 1a patients should be tested for the presence of nonstructural protein 5 (NS5A) resistance-associated polymorphisms. The likelihood of testing occurring in Canada and who would pay for it is unclear. If borne by provincial ministries of health, it will worsen cost-effectiveness, although the magnitude of this change and its impact on ICURs is unclear.
- Where polymorphisms are found, the treatment regimen changes to include RBV for 16 weeks even in treatment-naive patients. In the manufacturer's submission, all treatment-naive patients receive treatment for 12 weeks without RBV. No information has been submitted on the cost-effectiveness of an extended course of treatment in treatment-naive patients, but it would again reduce the cost-effectiveness of EBR/GZR.
- In treatment-experienced genotype 1a patients, the manufacturer's submission suggests 12-week treatment without RBV for treatment-experienced relapsers and 16 weeks of treatment with RBV for on-treatment virologic failures. It is unclear how much these categories overlap with those in the US recommendations; treatment-experienced patients may receive 12 or 16 weeks depending on NS5A status, and irrespective of the nature of treatment experience.
- A further category of patients (1a and 1b) relates to those who have received PR plus an HCV NS3/4A protease inhibitor, who would receive EBR/GZR plus ribavirin for 12 weeks. This has not been considered in the monograph.

For genotype 4 patients, the manufacturer's submission suggests treatment-experienced relapsers will receive 12 weeks of EBR/GZR, while treatment-experienced on-treatment failures receive 16 weeks of EBR/GZR plus RBV. In the US monograph, all treatment-experienced patients receive 16 weeks of EBR/GZR plus RBV. Any off-label use of the US recommendations in Canada is likely to worsen cost-effectiveness relative to the information provided.

4.1 Patient Input

Patient input was received from five patient groups. The general feedback received suggests that patients are concerned about:

- Pill burden associated with regimens
- Adverse events such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, insomnia, cognitive impairment, irritability, memory loss, headaches, hearing loss, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. These can affect patients' ability to participate in activities of daily living, which could lead to a burden on caregivers.
- Intolerance to some currently available treatment options.

The manufacturer has included adverse events in its model. Given the perspective of the analysis, the manufacturer did not account for caregiver burden in its model.

5. CONCLUSIONS

The comparative cost-effectiveness of EBR/GZR was assessed based on genotype, patients' treatment experience, and cirrhotic status. For treatment-naive and treatment-experienced groups in genotypes 1 (including 1a and 1b) and 4, this treatment provides a less expensive alternative to other new direct-acting antiviral agents for HCV. While EBR/GZR is less effective in some comparisons, the difference in costs is sufficient to suggest broad cost-effectiveness in these cases.

In genotype 3, the manufacturer is requesting funding for treatment-naive patients. In this case, the evidence suggests that at the confidential price provided, EBR/GZR is unlikely to be cost-effective. In order to obtain a cost-effectiveness ratio of ~$50,000 per QALY, a 26% to 44% price reduction would be required. The main driver for the difference between genotypes 3 and the other two genotypes considered here is the use of SOF alongside GZR and EBR in these subgroups.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 5 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 5: COST COMPARISON TABLE FOR DRUGS INDICATED FOR CHRONIC HEPATITIS C GENOTYPE 1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Elbasvir/ grazoprevir	**50/100 mg**	**Tab**	[redacted]	**50/100 mg daily**	**12 weeks[b]**	[redacted]	[redacted]
Elbasvir/ grazoprevir plus RBV	**50/100 mg**	**Tab**	[redacted][a]	**50/100 mg daily**	**16 weeks[c]**	[redacted]	[redacted]
	400 mg 600 mg		**14.5000 21.7500**	**800–1,400 mg daily**		**3,248 to 5,684**	
Interferon-free regimens							
Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi)	60 mg	Tab	428.57[d]	60 mg daily	12 to 24 weeks	$36,000	91,000 to 146,000
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
Ledipasvir/ Sofosbuvir (Harvoni)	90/400 mg	Tab	797.6190	90/400 mg daily	8 to 24 weeks[e]	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)
Ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (Holkira Pak)	12.5/75/ 50 mg 250 mg	3 Tabs	665.0000[f]	25/150/100 mg ombitasvir/ paritaprevir/ ritonavir daily and 250 mg dasabuvir twice daily	12 weeks[g]	55,860[b]	55,860
Ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (Holkira Pak) plus RBV	12.5/75/ 50 mg 250 mg	Tab	665.0000[f]	As above plus 1,000 to 1,200 mg/day RBV	12 to 24 weeks[g]	55,860[b]	55,860
	400 mg 600 mg		0.0001				

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Sofosbuvir (Sovaldi) plus RBV[d]	400 mg	Tab	654.7619	400 mg daily	24 weeks[h]	55,000 to 110,000	58,045 to 117,308
	400 mg 600 mg		14.5000 21.7500	1,000 to 1,200 mg daily		3,045 to 7,308	
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Cap	434.5500	150 mg daily	12 to 24 weeks[i]	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
Direct-acting antiviral agents in combination with peginterferon alfa plus RBV therapy							
Sofosbuvir (Sovaldi) plus PR	400 mg	Tab	654.7619	400 mg daily	12 weeks	55,000	59,750
	180 mcg/ 200 mg	Vial/Tab	395.8400	PegIFN 180 mcg/week; RBV 1,000 to 1,200 mg/day		4,750	
Simeprevir (Galexos) plus PR	150 mg	Cap	434.5500	150 mg daily	12 weeks	36,502	46,088 to 55,674
	180 mcg/ 200 mg	Vial/Tab	399.4100	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day	24 to 48 weeks[j]	9,586 to 19,172	
Boceprevir (Victrelis) plus PR	200 mg	Cap	12.5000	800 mg 3 times daily added after 4 weeks PR	24 to 44 weeks	25,200 to 46,200	37,475 to 67,243
	120 mcg/ 200 mg	Pens/ Caps	876.7800	PegIFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day[h]	28 to 48 weeks	12,275 to 21,043	
Boceprevir/ P2bR (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 mg/mcg/mg	168 Caps + 2 Pens + 56 Caps	2,652.55[k] 2,652.55[k] 2,726.00[k] 2,726.00[k]	Boceprevir 800 mg 3 times daily; PegIFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day, initiate after 4 weeks Pegetron therapy	24 to 44 weeks	31,831 to 59,972	31,831 to 59,972
Peginterferon alfa plus RBV therapy							
PegIFN alfa-2a + RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or Syringe/ 28 Tabs 35 Tabs 42 Tabs	399.4100	PegIFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[h]	48 weeks	19,172	19,172
PegIFN alfa-2b + RBV (Pegetron)	50 mcg/ 200 mg	2 Vials + 56 Caps	793.4700[k]	PegIFN 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[k]			21,115	21,115

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
	80 mcg/ 200 mg 100 mcg/ 200 mg 120 mcg/ 200 mg 150 mcg/ 200 mg	2 Pens/ 56 to 98 Caps	793.4700 793.4700 876.7800 879.7800			19,043 to 21,115	19,043 to 21,115

mcg = microgram; pegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
Note: All prices are from the Saskatchewan Drug Plan online formulary (Dec 2015) unless otherwise indicated.
[a] Manufacturer's confidential submitted price.
[b] 12 weeks for genotype 1 treatment-naive and treatment-experienced relapsers, as well as for treatment-experienced on-treatment virologic failure in patients with genotype 1b. Eight weeks can be considered in treatment-naive genotype 1b patients without significant fibrosis or cirrhosis.
[c] For genotype 1a patients with treatment-experienced on-treatment virologic failure.
[d] Price provided by Bristol-Myers Squibb for CADTH Hepatitis C Therapeutic Review report.[7]
[e] 12 weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. Eight weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA < 6 million IU/mL.
[f] List price is $665 per daily dose. Moderiba brand RBV is reimbursed at 0.0001 per tablet when used by Holkira Pak patients. When not provided free of charge, a 12- to 24-week course of RBV would cost $3,045 to $7,308 per patient.
[g] 12 weeks of Holkira Pak alone for patients with genotype 1b without cirrhosis; 12 weeks of Holkira Pak plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks of Holkira Pak plus RBV for patients with genotype 1a with cirrhosis who had previous null response to pegIFN and RBV.
[h] For treatment-naive and treatment-experienced non-cirrhotic patients with genotype 1 who are ineligible to receive an interferon.
[i] 12 weeks for treatment-naive, prior relapse patients, or prior non-responders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.
[j] 24 weeks for treatment-naive or prior relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. 48 weeks for treatment-naive or prior relapse patients with cirrhosis and HIV coinfection. 48 weeks for prior non-responders with or without cirrhosis and with or without HIV coinfection.
[k] Ontario Drug Benefit Exceptional Access Program (Nov 2015).

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

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
Elbasvir/ grazoprevir plus sofosbuvir (Sovaldi)	**100/50 mg**	**Tab**	[redacted]	**50/100 mg once daily**	**12 weeks**	[redacted]	[redacted]
	400 mg	Cap	654.7619	400 mg once daily		55,000	
Interferon-free regimens							
Daclatasvir (Daklinza) plus Sovaldi	60 mg	Tab	428.57[b]	60 mg once daily	12 to 24 weeks[c]	36,000 to 72,000	91,000 to 182,000
	400 mg	Cap	654.7619	400 mg once daily		55,000 to 110,000	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tab	654.7619	400 mg once daily	24 weeks	110,000	116,090 to 117,308
	400 mg 600 mg	Cap	14.5000 21.7500	1,000 to 1,200 mg daily		6,090 to 7,308	
Peginterferon alfa plus RBV therapy							
PegIFN alfa-2a + RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or Syringe/ 28 Tabs 35 Tabs 42 Tabs	399.4100	PegIFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[d]	48 weeks	19,172	19,172
PegIFN alfa-2b + RBV (Pegetron)	50 mcg/ 200 mg	2 Vials + 56 Caps	793.4700[d]	PegIFN 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[d]			21,115	21,115
	80 mcg/ 200 mg 100 mcg/ 200 mg 120 mcg/	2 Pens/ 56 to 98 Caps	793.4700 793.4700 876.7800 879.7800			19,043 to 21,115	19,043 to 21,115

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Cost for 1 Course of Combo Therapy ($)
	200 mg 150 mcg/ 200 mg						

mcg = microgram; pegIFN = 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.
[a] Manufacturer's confidential price.
[b] Price provided by Bristol-Myers Squibb for CADTH Hepatitis C Therapeutic Review report.[7]
[c] 12 weeks is for genotype 3 treatment-naive or treatment-experienced patients without cirrhosis. 24 weeks is for treatment-naive or treatment-experienced genotype 3 patients with compensated cirrhosis.
[d] Ontario Drug Benefit Exceptional Access Program (Dec 2015).

TABLE 7: 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 ($)
Elbasvir/ grazoprevir	**50/100 mg**	**Tab**	[redacted]	**50/100 mg once daily**	**12 weeks[b]**	[redacted]	[redacted]
Elbasvir/ grazoprevir plus RBV	**100/50 mg**	**Tab**	[redacted]	**50/100 mg once daily**	**16 weeks[c]**	[redacted]	[redacted]
	400 mg 600 mg		**14.5000 21.7500**	**800 mg to 1,400 mg daily**		**3,248 to 5,684**	
Interferon-free regimens[d]							
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Cap	434.5500	150 mg once daily	12 to 24 weeks[e]	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 antiviral agents in combination with peginterferon alfa plus RBV therapy							
Sovaldi (sofosbuvir) 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	PegIFN 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	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day	24 to 48 weeks[f]	9,586 to 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 plus RBV therapy							
PegIFN alfa-2a + RBV (Pegasys RBV)	180 mcg/ 200 mg	Vial or Syringe/ 28 Tabs 35 Tabs 42 Tabs	399.4100	PegIFN 180 mcg/week; RBV 1,000 to 1,200 mg/day[g]	48 weeks	19,172	19,172
PegIFN alfa-2b + RBV (Pegetron)	50 mcg/ 200 mg	2 Vials + 56 Caps	793.4700[h]	PegIFN 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[h]			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

mcg = microgram; pegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (Dec 2015) unless otherwise indicated.
[a] Manufacturer's confidential submitted price.
[b] 12 weeks for genotype 4 treatment-naive and treatment-experienced relapsers.
[c] For genotype 4 patients with treatment-experienced on-treatment virologic failure.
[d] Ombitasvir/paritaprevir/ritonavir (Technivie) is currently under review at CDR.
[e] 12 weeks for treatment-naive, prior relapse patients, or prior non-responders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.
[f] 24 weeks for treatment-naive or prior relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. 48 weeks for treatment-naive or prior relapse patients with cirrhosis and HIV coinfection. 48 weeks for prior non-responders with or without cirrhosis and with or without HIV coinfection.
[g] 48 weeks for Genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV coinfection.
[h] Ontario Drug Benefit Formulary, Exceptional Access Program (Dec 2015).

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 8: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	There are several places in which the detail provided by the manufacturer is less than ideal. While the assumptions used are clear, more detail on the reasons for these assumptions is necessary.		
Was the material included (content) sufficient?		X	
Comments	As above.		
Was the submission well organized and was information easy to locate?	X		
Comments			

TABLE 9: AUTHORS' INFORMATION

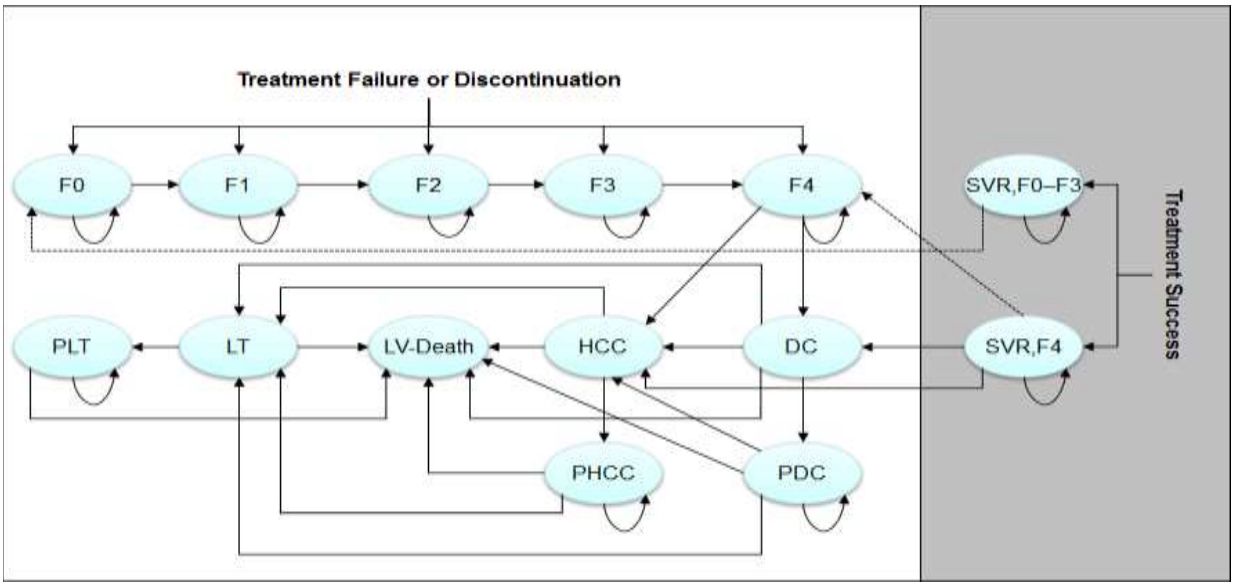
Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☒ Adaptation of Global model/Canadian model done by the manufacturer ☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model 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: MANUFACTURER'S MODEL STRUCTURE



The model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), two decompensated cirrhosis (DC) states—first year and subsequent years (PDC), two hepatocellular carcinoma (HCC) states—first year and subsequent years (PHCC), two liver transplant states—first year (LT) and subsequent years (PLT), liver-related death (Lv-Death), death from all other causes (not shown here), and two sustained virologic response (SVR) status states stratified by fibrosis stage – 'SVR, F0–F3' and 'SVR, F4'.
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 report text. Treatments are incorporated into this natural history by modifying the costs and utilities of the F0 to F4 and SVR F0 to F4 states 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.

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Data for efficacy was based on trial data (EBR/GZR) and published trial data (comparators), but the specific data informing each estimate are not provided. The methodology underlying the estimates is provided. Table 18 in the submission suggests data from 8 trials, of which 4 included Canadian patients.	The specific efficacy figures for EBR/GZR from the trials are not stated clearly.
Natural history	Data for fibrosis progression were based on the study from Thein and colleagues.[15] Adjustments were made for a higher fibrosis progression in GT 3.[16] Data for cirrhosis progression was based on a cohort of 384 cirrhotic patients,[17] as was the probability of mortality within hepatocellular carcinoma. Mortality for standard cases is based on Canadian life tables,[18,19] with excess mortality in DC was based on a cohort of 200 patients with DC.[20] Excess mortality following liver transplant was based on Wolfe.[21]	The manufacturers state that the natural history was cross-validated by comparing the probability of compensated cirrhosis at 20 years vs. other models, although relatively little detail is provided.
Utilities	A range of different papers using various measures of health are employed to estimate quality of life attached to each state. Utilities for health states F0 to F4 and SVR F0 to SVR F4 were based on HUI-2 data from Hsu et al.[8] All utilities were adjusted proportionally to reflect age-based norms for Canadian HUI-3 utilities,[9] although it is unclear how these were obtained from the information published in the source provided.[10] It was stated that utilities for decompensated cirrhosis were based on McLernon et al.,[11] but the figure used for DC (0.65) appears to differ from the estimated EQ-5D utility provided by that systematic review (0.79). An on-treatment disutility of 0.11 was assigned for treatments including pegylated interferon or RBV.[12]	The precise source and/or justification of several assumptions used in the model is unclear. The utilities generated by the assumptions in the model leads to some counterintuitive findings (see Limitations) below.
Resource use	There does not appear to be a specific section that deals with resource utilization separate from health state costs.	
AEs	AEs included were depression, anemia, and rash. For comparator interventions, these were taken from the CADTH Therapeutic Review report.[7] The source used for the EBR/GZR case is unclear.	The AE rates figures for EBR/GZR are unclear.
Costs		
Drug	Based on manufacturer list prices.	
AEs	Based on CADTH Therapeutic Review.[7]	
Health state	Based on Myers et al.[13]	

AE = adverse event; DC = decompensated cirrhosis; EBR = elbasvir; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; GT = genotype; GZR = grazoprevir; HUI-2 = Health Utilities Index Mark 2; RBV = ribavirin; SVR = sustained virologic response; vs. = versus.

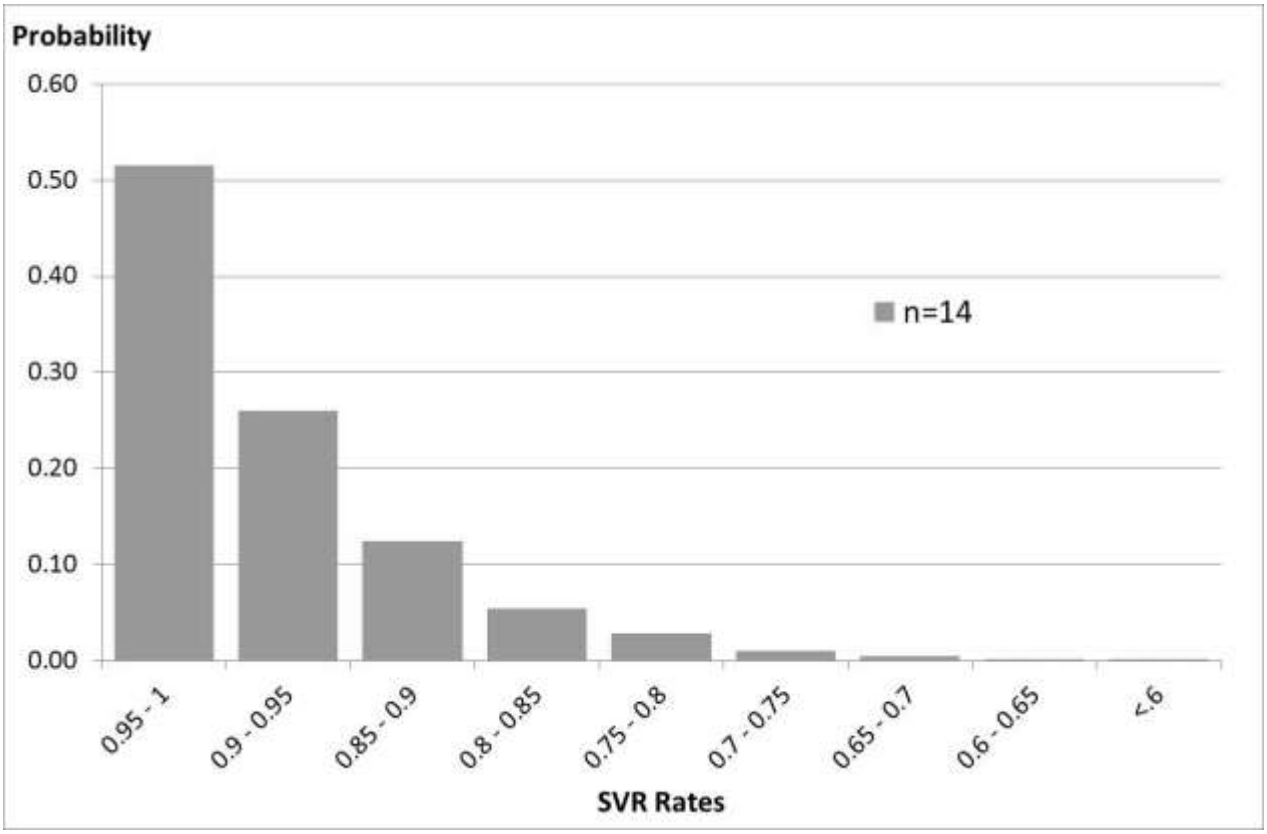
TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The model and follow-up period are modelled together. The first period of the model covers both the period in which treatment occurs (as an on-treatment utility) and the remaining period within the first year in which the patient is off-treatment.	While the first period is one year, discounting in this period assumes only that the on-treatment period has occurred. This also affects discounting in all subsequent years.
Patients in SVR F0, SVR F1, SVR F2, SVR F3 will not develop any further liver disease.	This assumption has been used elsewhere.
No spontaneous remission from chronic fibrosis (F0 to F4) states.	This assumption has been used elsewhere.
Progression to HCC and DC only occurs from states with compensated cirrhosis (F4, SVR F4) or DC (for HCC only).	This assumption has been used elsewhere.
Patients who receive a liver transplant are assumed to be at no risk of reactivation and progression to liver disease.	This assumption appears to be a simplification. However, liver transplantation is likely to occur in a small number of patients at a distant date. Any impact is likely to be minor.
Patient cohorts are defined according to age, gender, baseline fibrosis score, HCV genotype or subtype, viral load, HIV coinfection status, treatment history.	This greatly increases the complexity of the model. The way that this has been coded appears to have caused some issues. See "Reanalysis" section below.
Simpson's 1/3 rule used to adjust within-cycle correction, with a half-cycle correction as a sensitivity analysis.	See "Reanalysis" section below.
On-treatment disutility for all other treatments assumes no difference from baseline utility (F0 to F3).	No trial data appear to have been presented for health utilities for those receiving EBR/GZR, so the assumption appears unsupported.
Reinfection is possible from an SVR state.	This assumption is not always used but is a feature of the model. However, if reinfection occurs, it is assumed that patients return to the METAVIR F0 base state, rather than the state from which they entered SVR.
Uncertainty is incorporated where data suggest 100% efficacy in achieving SVR.	See below.

AE = adverse event; DC = decompensated cirrhosis; EBR = elbasvir; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; GT = genotype; GZR = grazoprevir; HCC = hepatocellular carcinoma; HUI-2 = Health Utilities Index Mark 2; RBV = ribavirin; SVR = sustained virologic response.

Where the clinical data for either EBR/GZR or a comparator treatment suggest 100% efficacy, the probabilistic sensitivity analysis (PSA) uses a modified uniform distribution in order to provide for some uncertainty. The justification for this approach is not made clear, but appears to be based on an assumption that while we have observed 100% efficacy, we do not know how likely it is that this would occur and a uniform prior is assumed for this, which is then used to estimate a probability for efficacy. This leads to relatively conservative inputs in the modelling process and appears to be a pragmatic way to deal with data limitations. As an example, the genotype 3 treatment-naive non-cirrhotic case included 14 patients, each of whom responded to treatment (achieved SVR). The base-case SVR rate here is 100%, with the distribution used in the PSA using a random number raised to the power 1/14 (i.e., the binomial distribution). This leads to a distribution with a 95% confidence interval (CI) of 0.77 to 1.00, with the distribution as appears in Figure 2. Overall, the manufacturer's approach appears to be a pragmatic solution to the issue of little data versus high certainty.

FIGURE 2: SUSTAINED VIROLOGIC RESPONSE PARAMETER DISTRIBUTION WHERE N = 14 PATIENTS ALL RESPONDED TO TREATMENT



SVR = sustained virologic response.

Manufacturer's Results

For genotype 1, the manufacturer's submission considers EBR/GZR alongside both No Treatment and six other active treatments (PR, SIM+PR, SOF+PR, OMB/PAR/RIT+DAS ± RBV, SIM+SOF, and LDV/SOF). For the sake of brevity, outcomes for the options that are either weakly dominated (by extended dominance) or dominated are removed in Table 12.

TABLE 12: MANUFACTURER'S RESULTS FOR EBR/GZR GENOTYPE 1 PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Treatment-naive, non-cirrhotic					
No Treatment	16,028	9.64			
EBR/GZR	41,118	11.58	25,090	1.95	12,887
LDV/SOF	54,738	11.66	13,620	0.08	177,184
Treatment-naive, cirrhotic					
No Treatment	33,036	6.93			
EBR/GZR	50,801	10.65	17,765	3.72	4,778
LDV/SOF	72,637	10.66	21,836	0.00	4,707,428
Treatment-experienced, non-cirrhotic					
No Treatment	17,020	9.49			

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
EBR/GZR±RBV	53,557	11.54	36,537	2.05	17,834
OMB/PAR/RIT+DAS± RBV	60,068	11.62	6,511	0.08	79,581
Treatment-experienced, non-cirrhotic					
No Treatment	33,036	6.93			
EBR/GZR±RBV	57,918	10.72	24,882	3.79	6,752

DAS = dasabuvir; EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/RIT+DAS ± RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

In all four of these cases, EBR/GZR–containing regimens are suggested to become the most cost-effective option at relatively low values per QALY, with this ICUR ranging from $4,778 per QALY to $17,834. These regimens are suggested to be cost-effective up to and beyond $50,000 per QALY, with either LDV/SOF or OMB/PAR/RIT+DAS ± RBV more effective (by around 0.08 QALYs) in three of the four cases. The only one of these cases in which the more effective comparator seems potentially cost-effective is the Treatment-Experienced, Non-Cirrhotic case in which OMB/PAR/RIT+DAS ± RBV becomes cost-effective at around $80,000 per QALY.

For genotype 3, the manufacturer's model provides outcomes for treatment-naive groups (Table 13). In both of these cases, EBR/GZR is compared within the sequential analysis against PR and has an ICUR exceeding $50,000 per QALY. Note, SOF/RBV was dominated by EBR/GZR.

TABLE 13: MANUFACTURER'S RESULTS FOR EBR/GZR GENOTYPE 3 PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Treatment-naive, non-cirrhotic					
No Treatment	19,052	9.20			
PR	24,720	10.55	5,668	1.35	4,199
EBR/GZR	98,742	11.66	74,022	1.11	66,933
Treatment-naive, cirrhotic					
No Treatment	33,036	6.93			
PR	34,634	8.89	1,598	1.95	818
EBR/GZR	108,119	10.08	73,485	1.19	61,527

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

For genotype 4, the manufacturer provides comparisons for treatment-naive and treatment-experienced cases (Table 14). In the case of treatment-naive, non-cirrhotic patients, all four comparators appear cost-effective for at least some values of the cost-effectiveness threshold. However, EBR/GZR again provides an ICUR below $50,000, and while SOF+PR is more effective, its ICUR exceeds $200,000 per QALY. In the remaining cases, EBR/GZR (with RBV in the Treatment-Experienced scenarios) is stated to be the most effective treatment and dominates against the other active comparators (PR and SOF+PR). In each of these cases, the ICUR against No Treatment is well below $50,000 per QALY, suggesting cost-effectiveness.

TABLE 14: MANUFACTURER'S RESULTS FOR EBR/GZR GENOTYPE 4 PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Treatment-naive, non-cirrhotic					
No Treatment	16,028	9.64			
PR	24,421	10.58	8,393	0.95	8,854
EBR/GZR	45,556	11.61	21,135	1.02	20,676
SOF+PR	63,241	11.69	17,685	0.08	208,971
Treatment-naive, cirrhotic					
No Treatment	33,036	6.93			
EBR/GZR	50,214	10.74	17,178	3.81	4,514
Treatment-experienced, non-cirrhotic					
No Treatment	17,020	9.49			
EBR/GZR±RBV	56,265	11.66	39,245	2.17	18,106
Treatment-experienced, cirrhotic					
No Treatment	33,036	6.93			
EBR/GZR±RBV	61,488	10.71	28,452	3.78	7,534

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio, PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

The sensitivity analyses provided within the model are (1) additional "secondary" analyses conducted with the model in other subgroups, (2) univariate sensitivity analyses varying each model parameter in turn, and (3) probabilistic sensitivity analyses.

Secondary Analyses

Five additional analyses are presented as "secondary" to the base case:

- Genotype 1b, Treatment-Naive F0 to F2 patients. Table 15 provides a summary of the closest case within the base-case results with the first secondary analysis, which considers METAVIR stages F0 to F2 with those infected by the HCV genotype 1b subtype. Although not explicitly stated, this appears to be the case in which an eight-week treatment regimen is considered. As in the existing base case, EBR/GZR appears cost-effective, although it is noticeable that the effectiveness of EBR/GZR, LDV/SOF, and OMB/PAR/RIT+DAS ± RBV has changed within this analysis.
- For genotype 1a, the results for the treatment-experienced on-treatment virologic failures group are presented separately. This group receives a 16-week treatment with EBR/GZR rather than the 12 weeks of most other groups. In this case, the results suggest that EBR/GZR is *dominated* by OMB/PAR/RIT+DAS ± RBV within this group, as it is both more expensive and provides fewer QALYs. It is worth noting that the results for the genotype 1a groups, other treatment failures subgroup are combined with results for other subgroups to form the aggregated results for genotype 1 in Table 12. If the indication for genotype 1 had not included this group or funding is considered that does not include this group, it would be more cost-effective than shown ($17,834 per QALY).
- A second "other treatment failures" set of results is provided for genotype 4. In this case, the ICUR for this group versus No Treatment is $19,153 per QALY. This is slightly higher than the figures for the non-cirrhotic ($18,106 per QALY) and cirrhotic ($7,534 per QALY) subgroups shown in Table 14, but this is unlikely to affect any overall judgment of cost-effectiveness as this seems to be clear (from the manufacturer's results) in all cases.

- Figures are also provided for genotype 1 treatment-naive, HIV-positive patients that suggest EBR/GZR is cost-effective whether the patient is non-cirrhotic ($10,307 per QALY vs. No Treatment) or cirrhotic ($4,683 per QALY vs. No Treatment).

TABLE 15: MANUFACTURER'S RESULTS FOR GENOTYPE 1B, F0 TO F2 PATIENTS PLUS CLOSEST BASE-CASE RESULTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Genotype 1b, treatment-naive, F0 to F2 (secondary)					
No Treatment	13,735	9.98			
PR	25,543	10.42	Ext. Dominated		
LDV/SOF	54,676	11.67	Dominated by EBR/GZR		
EBR/GZR	30,863	11.67	17,128	1.69	10,110
OMB/PAR/RIT+DAS± RBV	57,310	11.67	26,447	0.00	16,574,316
Genotype 1, treatment-naive, F0 to F3 (from base case)					
No Treatment	16,028	9.64			
EBR/GZR	41,118	11.58	25,090	1.95	12,887
OMB/PAR/RIT+DAS± RBV	59,534	11.62	Dominated by LDV/SOF		
LDV/SOF	54,738	11.66	13,620	0.08	177,184

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; PR = pegylated interferon plus ribavirin; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Univariate Sensitivity Analyses

A large number of additional univariate analyses are considered, although as these changes affect only one parameter at a time, they do not provide a great deal of additional information.

Genotype 1: While there is not a comparison shown for the ICURs between EBR/GZR and No Treatment (which is relevant within Table 12), tables are provided showing the effect of parameter changes on ICURs for EBR/GZR and LDV/SOF. This is a relevant consideration for the Treatment-Naive cases, and here it appears that while there are some large differences in ICURs as a result of univariate changes, the only change that would result in an ICUR below $100,000 per QALY was a change in the discount rate applied to QALYs — and this is a methodological issue rather than a question of the evidence base.

For the treatment-experienced, non-cirrhotic case, a main issue is the ICUR between cost-effectiveness versus OMB/PAR/RIT+DAS ± RBV. With the exception of the discount rate to be applied to QALYs, the only change able to provide an ICUR below $50,000 related to the parameter representing the proportion of genotype 1a on-treatment virologic failure patients within this sample. In the base case, this proportion is 41% and the ICUR is $79,581; where it increases to 52%, the ICUR falls to $37,340 per QALY.

Genotype 3: In this case, the relevant ICUR is between PR and EBR/GZR. Aside from discount rates, the only figures able to generate an ICUR for EBR/GZR below $50,000 were (1) a higher SVR for EBR/GZR from F4 (to 99.2%), which leads to an ICUR of $39,635 per QALY; (2) a lower regimen cost for EBR/GZR (to $2,750), which leads to an ICUR of $41,203 per QALY; and (3) a higher probability of hepatocellular carcinoma from compensated cirrhosis (F4) (to 7.9% per year), which leads to an ICUR of $47,901 per QALY.

Genotype 4: As with genotype 1, the ICURs provided in the sensitivity analyses (PR vs. EBR/GZR) are not generally informative, as they do not show the ICUR for No Treatment versus EBR/GZR (with RBV for treatment-experienced patients), which appears to be the main comparison of interest. For the treatment-naive, non-cirrhotic subgroup (in which EBR/GZR is sequentially compared with PR in the main analysis), none of the changes considered in the univariate analyses would lead to an ICUR for EBR/GZR higher than 31,352 per QALY, and so it appears to remain cost-effective.

Probabilistic Sensitivity Analyses
Probabilistic sensitivity analyses are provided by the manufacturer, but due to the method used to generate their results, it seems likely that they can correctly characterize uncertainty in the results. As a result, they are not presented.

CADTH Common Drug Review Reanalyses

Several concerns are raised regarding the manufacturer's submission.

(1) Issues in the Construction/Coding of the Manufacturer's Submitted Excel Model
Complexity: The most critical concern is with respect to the complexity of the manufacturer's model. This complexity means that the model takes around 12 hours to run a single probabilistic sensitivity analysis involving only 1,000 iterations. This is due to the model calculating results across 154 scenarios defined by genotype, prior exposure to treatment, and cirrhosis status for each of 12 different demographic groups (based on six ages and male/female gender). This means that a total of 1,848 distinct models are computed, within each of which there are 1,000 model runs; i.e., each time any change is made to the parameters and the model is rerun (e.g., for exploratory purposes), this requires the Markov process to run nearly 2 million times. It is not possible within the implementation of the model provided by the manufacturer to run results for only a single subgroup and this would have limited the ability of CDR to assess the model and make any desired changes.

Use of data tables: The method used to construct the model in Excel uses data tables. These tables allow a range of scenarios to be computed with a minimum of effort, but do so by calculating results separately for a number of submodels, which are then subsequently used to construct a probabilistic sensitivity analysis by taking a weighted average across these models. Each of these subgroups represents a clinical subgroup based on the type of HCV and prior exposure (plus response status, where applicable), age, and gender. For the "Genotype 1, Treatment-Naive, Non-Cirrhotic" case, this means that there are four subgroups (representing high viral load genotype 1a patients, low viral load genotype 1a patients, high viral load genotype 1b patients, and low viral load genotype 1b patients) and 12 demographic groups within these. In this case, the model results presented above are based on 48 distinct models.

The difficulty here has less to do with the complexity than that the (up to 48) different models are not necessarily comparable. Many parameters (e.g., relating to natural history) should be identical across the demographic groups and/or the patient subgroups, unless there is a very specific reason why this should not be the case. However, in many places it appears that because data tables are used, the parameters used to form a total cost estimate appear to be obtained independently of the parameters informing total benefits within a subgroup, and that for the same model iteration, the figures for each subgroup will be also be obtained independently of each other. As a result, it seems unlikely that the probabilistic sensitivity analysis will correctly represent uncertainty.

Use of random numbers: The manufacturer's model does not attempt to use random numbers when constructing probabilistic sensitivity analysis results. Instead, the random number generator uses the *same* starting value (seed) each time the macro runs, and every subsequent number is then based on the previous random number used. This means that exactly the same values will be obtained every time the manufacturer's model is used, for a given set of starting values. As a result, it is not possible to assess within the provided model how stable the results of the evaluation are, because every time it is rerun, it should in principle provide exactly the same results.

Use of Simpson's 1/3 rule: The submitted model bases its results on Simpson's 1/3 rule to adjust for timing of events within periods, as opposed to the half-cycle correction. While this is not entirely novel, it remains a non-standard approach, and if used, should have appeared as a sensitivity analysis. This is particularly the case as the requirements for using the Simpson's rule (equal-sized subintervals, even number of intervals) are not met, as the first period of the model reflects treatment time (shorter than all other periods); the Markov model allows up to 101 cycles. The impact of using Simpson's rule where these requirements are not met is unclear.

CADTH Common Drug Review Reanalysis

Given the concerns relating to the manufacturer's model, CDR focused on replicating the manufacturer's approach and results in a validation exercise. In a reconstruction of the model, the same assumptions are used except as relates to the points above:

- In order to reduce the time that the original model takes to run, the reconstructed model does not use the 12 demographic subgroups of the original model. Instead, based on feedback from the Clinical Advisor as to appropriate parameter values, the model uses a simulated cohort of 45-year-olds, of whom 60.5% are male (as per the manufacturer assumption). Mortality in each period is a weighted average of the gender-specific mortalities provided in order to approximate the mortality in a cohort containing of both genders.
- The reconstructed model uses spreadsheets based on the specific decision problems and involves up to four subgroups for each parameter. Within the reconstructed model, the parameters are sampled and then used to obtain costs and benefits for all subgroups at the same time, which are then averaged.
- The half-cycle correction is used in preference to Simpson's 1/3 rule.
- Random numbers are used without defining an arbitrary "seed" value for the random number generator, so that each run of the model may be different and can indicate likely convergence.
- A total of 10,000 model runs are used rather than the 1,000 used by the manufacturer. Given that the model runs significantly more quickly (and can focus on a single decision problem), this increased precision is achievable.

(2) Reporting of Methodology is Incomplete

The reporting of utility figures in the manufacturer's write-up left the justification for many assumptions unclear to the CDR reviewers. This is problematic, as some of the figures in the model are counterintuitive. Within the model, for example, the increase in utility attached to obtaining SVR is 0.02 for SVR F0 to F3 (compared with F0 to F3) and 0.07 for SVR F4 (compared with F4). With greater cirrhosis, it seems potentially plausible that the removal of active infection may have a greater utility effect. However, the addition of this figure means that the utility for SVR F4 is typically higher than that which obtains for SVR F0 to F3, so that those with compensated cirrhosis are healthier than those with fibrosis but no compensated cirrhosis.

The efficacy and adverse event data for EBR/GZR are stated, but the level of detail is not ideal, as it is not simple to verify the specific assumptions used without knowing how they are obtained.

CADTH Common Drug Review Reanalysis

In addition to the reconstructed model, CDR also explored the impact of using alternative utility estimates for states in the natural history model (i.e., F0 to F4, decompensated cirrhosis, liver transplant, hepatocellular carcinoma) using Chong et al.[22] This paper was used in the 2007 CADTH evaluation of peginterferon and ribavirin.[23]

(3) Treatment of Reinfection

The method by which reinfection is incorporated within the model is counterintuitive. In the model, states are defined according to the METAVIR classification. In the event that a patient with some element of fibrosis short of compensated cirrhosis (i.e., F0 to F3) achieves SVR, then he or she will enter into a state corresponding to that METAVIR state (i.e., as SVR F0, SVR F1, SVR F2, or SVR F3). If reinfection occurs following achievement of SVR, the patient is assumed to re-enter the non-SVR fibrosis states in F0. This suggests that a patient with portal fibrosis with numerous septa without cirrhosis (F3) could achieve SVR in the following cycle (year) with the same fibrosis status (SVR F3), but on reinfection the fibrosis would automatically disappear (F0).

CADTH Common Drug Review Reanalysis

While this does not seem credible, the numbers of patients who experience reinfection are likely to be relatively low, and so this was not modified in the CDR reanalysis as an additional analysis.

Other Changes Made in CDR Reanalysis

- Price reduction scenarios. For those cases in which EBR/GZR is not cost-effective, price reduction scenarios are used to identify the reduction necessary to obtain an ICUR of $50,000 per QALY. A standard series of discounts to 50% (in 10% increments) is considered alongside additional scenarios necessary to obtain the targeted ICUR.
- Based on clinical feedback, the CDR reviewers also attempt to split results for genotype 1a and genotype 1b using the manufacturer's modelled subgroups as far as is practicable. This means that instead of providing results for genotype 1-based treatment-naive groups, separate results are presented for both genotype 1a and genotype 1b. For the treatment-experienced groups, the manufacturer model provides scenarios for both genotype 1a relapsers and other treatment failures (non-relapsers with genotype 1a and all genotype 1b). As neither of these groups is a "pure" genotype 1a or genotype 1b, the treatment-experienced groups are combined as per the manufacturer model. As a result, the CDR reanalyses consider treatments in the following 12 subgroups:
  (1) Genotype 1a, treatment-naive, non-cirrhotic
  (2) Genotype 1b, treatment-naive, non-cirrhotic
  (3) Genotype 1a, treatment-naive, cirrhotic
  (4) Genotype 1b, treatment-naive, cirrhotic
  (5) Genotype 1, treatment-experienced, non-cirrhotic
  (6) Genotype 1, treatment-experienced, cirrhotic
  (7) Genotype 3, treatment-naive, non-cirrhotic
  (8) Genotype 3 treatment-naive, cirrhotic
  (9) Genotype 4, treatment-naive, non-cirrhotic
  (10) Genotype 4, treatment-naive, cirrhotic
  (11) Genotype 4, treatment-experienced, non-cirrhotic
  (12) Genotype 4, treatment-experienced, cirrhotic.

Revised Results Based on Reconstructed Model (CADTH Common Drug Review Baseline)

Results for the genotypes 1 subgroups (including 1a and 1b) are provided in Table 16; the analyses produced broadly similar results to the manufacturer's findings shown in Table 14.

For the treatment-experienced, non-cirrhotic subgroup, the ICUR for OMB/PAR/RIT+DAS ± RBV versus EBR/GZR is lower, at $59,684 per QALY compared with around $80,000 per QALY within the manufacturer's model (Table 17). However, EBR/GZR appears to be the option that is most likely to be cost-effective at $50,000 per QALY. Based on the probabilistic sensitivity analysis, there is a 63% likelihood of cost-effectiveness for EBR/GZR (vs. 37% likelihood for OMB/PAR/RIT+DAS ± RBV). For the cirrhotic subgroup, the ICUR for EBR/GZR versus No Treatment is again below $10,000 per QALY, but LDV/SOF would become cost-effective at very high ICURs (above $500,000 per QALY).

As with the presentation of the manufacturer's base case, treatments that are dominated (whether directly or through extended dominance) are not displayed in the table for reasons of brevity. For the new treatment-naive cases, there does not seem to be much of a question around cost-effectiveness in the CDR baseline, with EBR/GZR appearing cost-effective in a range extending both below and above $50,000 per QALY. In these cases, the ICUR for EBR/GZR appears to be slightly lower than the corresponding ICUR that might be expected based on the manufacturer's base case. The only notable difference is that OMB/PAR/RIT+DAS ± RBV appears to provide a higher number of QALYs than EBR/GZR in the cirrhotic cases, whereas in the manufacturer's case, the opposite case held true.

TABLE 16: CADTH COMMON DRUG REVIEW REANALYSIS FOR EBR/GZR GENOTYPE 1 PATIENTS, TREATMENT-NAIVE

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Genotype 1A, treatment-naive, non-cirrhotic					
No Treatment	17,185	9.90			
PR	27,607	10.96	10,423	1.06	9,838
EBR/GZR	46,165	11.99	18,558	1.03	17,951
LDV/SOF	54,887	12.08	8,723	0.09	94,202
Genotype 1A, treatment-naive, cirrhotic					
No Treatment	34,935	7.15			
EBR/GZR	52,064	10.99	17,130	3.84	4,463
LDV/SOF	73,427	11.06	21,363	0.07	302,427
Genotype 1B, treatment-naive, non-cirrhotic					
No Treatment	17,160	9.90			
EBR/GZR	34,724	12.07	17,564	2.17	8,098
OMB/PAR/RIT+DAS±RBV	57,455	12.12	22,731	0.06	407,827
Genotype 1B, treatment-naive, cirrhotic					
No Treatment	34,861	7.16			
PR	41,924	8.70	7,062	1.54	4,593
EBR/GZR	52,602	10.90	10,678	2.20	4,844
LDV/SOF	73,335	11.06	20,733	0.16	128,196

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

TABLE 17: CADTH COMMON DRUG REVIEW REANALYSIS FOR EBR/GZR GENOTYPE 1 PATIENTS, TREATMENT-EXPERIENCED

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Genotype 1, treatment-experienced, non-cirrhotic					
No Treatment	18,358	9.76			
EBR/GZR	54,024	11.97	35,666	2.21	16,136
OMB/PAR/RIT+DAS ± RBV	60,222	12.07	6,198	0.10	59,684
LDV/SOF	68,341	12.07	8,119	0.00	4,991,543
Genotype 1, treatment-experienced, non-cirrhotic					
No Treatment	34,981	7.15			
EBR/GZR	60,850	10.83	25,869	3.67	7,040
OMB/PAR/RIT+DAS ± RBV	75,747	10.97	14,896	0.14	105,958
LDV/SOF	140,495	11.08	64,748	0.12	562,014

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir.

For the genotype 3 treatment-naive cases (Table 18), the analyses produced broadly similar results to the manufacturer's findings (Table 13), in that EBR/GZR does not appear cost-effective at $50,000 per QALY for patients in either case. The magnitude of the ICUR for EBR/GZR is higher in the CDR base case, at $115,659 per QALY (vs. $66,933 per QALY) in the non-cirrhotic case and $75,305 per QALY (versus $61,527 per QALY) in the cirrhotic case. This has occurred largely because the QALYs attached to PR appear to be larger in the CDR reanalysis.

TABLE 18: CADTH COMMON DRUG REVIEW REANALYSIS FOR EBR/GZR GENOTYPE 3 PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Treatment-naive, non-cirrhotic					
No Treatment	20,308	9.47			
PR	25,399	11.29	5,092	1.81	2,807
EBR/GZR	100,117	11.93	74,718	0.65	115,659
Treatment-naive, cirrhotic					
No Treatment	34,962	7.16			
PR	36,357	9.52	1,395	2.36	592
EBR/GZR	109,041	72,685	0.97	1.19	75,305

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year.

In terms of the likelihood of cost-effectiveness, the cost-effectiveness acceptability curve (CEAC) for the non-cirrhotic case suggests a virtual certainty that PR is the most cost-effective option at $50,000 per QALY, while for the cirrhotic case there is only a 19% chance that EBR/GZR is cost-effective at $50,000 per QALY.

Finally, for genotype 4, the manufacturer results suggested that EBR/GZR would be cost-effective at $50,000 per QALY regardless of prior treatment exposure and cirrhosis status. The same general results are obtained in the CDR reanalysis; however, as in previous cases, the number of options that might be considered cost-effective under some circumstances (or values per QALY) has again increased. In particular, the ICURs for PR versus No Treatment and EBR/GZR vs. PR are very similar in three of the four cases.

TABLE 19: CADTH COMMON DRUG REVIEW REANALYSIS FOR EBR/GZR GENOTYPE 4 PATIENTS

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
Treatment-naive, non-cirrhotic					
No Treatment	17,195	9.91			
PR	25,111	11.32	7,916	1.41	5,614
EBR/GZR	45,724	12.06	20,613	0.74	27,927
SOF + PR	63,814	12.07	18,090	0.01	1,314,135
Treatment-naive, cirrhotic					
No Treatment	34,826	7.15			
PR	42,307	8.63	7,481	1.48	5,047
EBR/GZR	54,750	10.59	12,443	1.96	6,359
SOF + PR	123,032	10.64	68,281	0.05	1,399,911
Treatment-experienced, non-cirrhotic					
No Treatment	18,293	9.75			
PR	31,500	10.48	13,207	0.73	18,086
EBR/GZR±RBV	58,486	11.84	39,245	2.17	19,931
Treatment-experienced, cirrhotic					
No Treatment	34,752	7.15			
PR	44,304	8.41	9,552	1.26	7,599
EBR/GZR±RBV	65,720	10.62	21,416	2.21	9,695

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

In general, there appears to be relatively little uncertainty as to cost-effectiveness at $50,000 per QALY in three of the four cases, with at least a 90% likelihood of cost-effectiveness for EBR/GZR. The only remaining case relates to the treatment-experienced, non-cirrhotic case, for which there is around a 74% likelihood of cost-effectiveness for EBR/GZR with the remaining 26% likelihood attached to SOF/RBV. While SOF/RBV is dominated in terms of the overall expected costs and expected QALY figures, there is clearly still some significant uncertainty as to whether it may still be the most cost-effective option over a wide range of values for the cost-effectiveness threshold.

Effects of Alternative Utility Values

In order to test for the effects of alternative utility values, the model was rerun for the genotype 1a and 1b cases. While there are some differences, these appear to be relatively minor, and so the choice of utility estimates does not appear to be a major driver of results in the model.

TABLE 20: SEQUENTIAL INCREMENTAL COST-UTILITY RATIOS FOR GENOTYPE 1 CASES WITH ALTERNATIVE UTILITY VALUES

	ICURs ($/QALY)	
ICURS	**Base Case**	**Alternative**
Genotype 1A, TN non-cirrhotic		
No Treatment		
PR	9,838	13,659
EBR/GZR	17,951	17,520
LDV/SOF	94,202	110,848
Genotype 1A, TN cirrhotic		
No Treatment		
EBR/GZR	4,463	4,845
LDV/SOF	302,427	329,693
Genotype 1B, TN non-cirrhotic		
No Treatment		
EBR/GZR	8,098	10,259
OMB/PAR/RIT+DAS±RBV	407,827	571,107
Genotype 1B, TN cirrhotic		
No Treatment		
PR	4,593	(ext. dominance)
EBR/GZR	4,844	5,117
LDV/SOF	128,196	135,102

EBR = elbasvir; GZR = grazoprevir; ICUR = incremental cost-utility ratio; LDV = ledipasvir; OMB/PAR/RIT+DAS±RBV = ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir; TN = treatment-naive.

Price Reduction Scenarios

Within the model, EBR/GZR appears to be cost-effective except within genotype 3, in which the CDR reanalyses suggest that the ICURs for the non-cirrhotic ($115,659 per QALY) and cirrhotic ($75,305 per QALY) are significantly higher than an indicative figure of $50,000 per QALY. CDR ran a series of price reduction scenarios to assess the size of reduction likely to be necessary in order for EBR/GZR to be considered cost-effective within these patient subgroups. For the non-cirrhotic case, a 44% price reduction produces an ICUR of $49,222 per QALY versus PR (incremental cost $31,965, incremental QALYs 0.65). For the cirrhotic case, a 26% price reduction produces an ICUR of $49,571 per QALY versus PR (incremental cost $47,503, incremental QALYs 0.96). The other scenarios considering discounts to 50% (in 10% increments) appear Table 4.

REFERENCES

1. Zepatier (grazoprevir/elbasvir): 100 mg/50 mg tablets [product monograph]. Kirkland (QC): Merck Canada Inc.; 2016 Jan 19.
2. CDR submission: grazoprevir/elbasvir tablets 100 mg/50 mg. Company: Merck Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Kirkland (QC): Merck Canada Inc.; 2015 Oct 27.
3. Pharmacoeconomic evaluation. In: CDR submission: grazoprevir/elbasvir tablets 100 mg/50 mg. Company: Merck Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Kirkland (QC): Merck Canada Inc.; 2015 Oct 27.
4. Chhatwal J, Ferrante SA, Brass C, El Khoury AC, Burroughs M, Bacon B, et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. Value Health [Internet]. 2013 Sep [cited 2016 Feb 25];16(6):973-86. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820000
5. Ferrante SA, Chhatwal J, Brass CA, El Khoury AC, Poordad F, Bronowicki JP, et al. Boceprevir for previously untreated patients with chronic hepatitis C genotype 1 infection: a US-based cost-effectiveness modeling study. BMC Infect Dis [Internet]. 2013 [cited 2016 Feb 25];13:190. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643851
6. Elbasha EH, Chhatwal J, Ferrante SA, El Khoury AC, Laires PA. Cost-effectiveness analysis of boceprevir for the treatment of chronic hepatitis C virus genotype 1 infection in Portugal. Appl Health Econ Health Policy. 2013 Feb;11(1):65-78.
7. Drugs for chronic hepatitis C infection -- cost-effectiveness analysis (Draft for consultation) [Internet]. Ottawa: CADTH; 2015 Jul. [cited 2016 Feb 25]. (CADTH Therapeutic review). Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Hep_C_PE_Report.pdf
8. Hsu PC, Federico CA, Krajden M, Yoshida EM, Bremner KE, Anderson FH, et al. Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection. J Gastroenterol Hepatol. 2012 Jan;27(1):149-57.
9. Maddigan SL, Feeny DH, Johnson JA. Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey. Qual Life Res. 2005 Jun;14(5):1311-20.
10. Wong WW, Tu HA, Feld JJ, Wong T, Krahn M. Cost-effectiveness of screening for hepatitis C in Canada. CMAJ [Internet]. 2015 Feb 17 [cited 2016 Feb 25];187(3):E110-E121. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4330166
11. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008 Jul;28(4):582-92.
12. Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess [Internet]. 2006 Jul [cited 2016 Feb 25];10(21):1-113, iii. Available from: http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-21
13. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol [Internet]. 2014 May [cited 2016 Feb 1];28(5):243-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049256
14. Statistics Canada [Internet]. Ottawa: Statistics Canada; 2016 Feb 8. Consumer price index, health and personal care, by province (monthly) (Newfoundland and Labrador); 2016 Feb 19 [cited 2016 Feb 25]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/cpis13a-eng.htm

15. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.

16. Probst A, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. J Viral Hepat. 2011 Nov;18(11):745-59.

17. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997 Feb;112(2):463-72.

18. Statistics Canada [Internet]. Ottawa: Statistics Canada; 2016 Feb 8. Table 1b. Complete life table, females, Canada, 2009 to 2011; 2015 Nov 30 [cited 2016 Feb 25]. Available from: http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl/tbl1b-eng.htm

19. Statistics Canada [Internet]. Ottawa: Statistics Canada; 2016 Feb 8. Table 1a. Complete life table, males, Canada, 2009 to 2011; 2015 Nov 30 [cited 2016 Feb 25]. Available from: http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl/tbl1a-eng.htm

20. Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 2004 May;40(5):823-30.

21. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. Am J Transplant. 2010 Apr;10(4 Pt 2):961-72.

22. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. 2003 Mar;98(3):630-8.

23. Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, et al. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Internet]. Ottawa: CADTH; 2007. [cited 2016 Feb 25]. (Technology report no. 82). Available from: https://www.cadth.ca/sites/default/files/pdf/232_HepC_tr_e.pdf