Common Drug Review

Pharmacoeconomic Review Report

November 2016

Drug	simeprevir (Galexos) (150 mg)
Indication	chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin in adults with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon therapy (pegylated or non-pegylated) with ribavirin
Listing request	List with similar criteria to the other currently marketed protease inhibitors (boceprevir and telaprevir) in line with its Health Canada indication.
Manufacturers	Janssen Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CMA	cost-minimization analysis
CrI	credible interval
CUA	cost-utility analysis
DAA	direct-acting antiviral
DB	double-blind
DCC	decompensated cirrhosis
EQ-5D	EuroQol 5-Dimensions questionnaire
FDA	US Food and Drug Administration
FIX	fixed-treatment regimen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HUI	Health Utilities Index
LT	liver transplant
NMA	network meta-analysis
OR	odds ratio
pLT	post-liver transplant
PR	peginterferon alfa plus ribavirin
RGT	response-guided therapy
SVR	sustained virologic response
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Simeprevir (Galexos)
Study question	"From the perspective of the provincial Ministry of Health, what is the incremental cost-effectiveness of simeprevir in treatment of CHC infection compared with boceprevir and telaprevir and standard therapy with peginterferon and ribavirin?"
Type of economic evaluation	CUA
Target population	CHC genotype 1 treatment-naive or treatment-experienced patients considered suitable candidates for simeprevir therapy.
Treatment	Simeprevir 150 mg daily for 12 weeks in combination with peginterferon and ribavirin for 24 or 48 weeks
Outcome(s)	LYs gained QALYs gained
Comparators	• Telaprevir plus PR • Boceprevir plus PR • PR alone
Perspective	Ministry of Health perspective
Time horizon	Lifetime (approximately 68 years)
Manufacturer's results (base case)	**Treatment-naive:** • Simeprevir plus PR versus PR: $32,497/QALY • Simeprevir plus PR versus telaprevir plus PR: Dominant • Simeprevir plus PR versus boceprevir plus PR: $5,202/QALY **Treatment-experienced:** • Simeprevir plus PR versus PR: $20,430/QALY • Simeprevir plus PR versus telaprevir plus PR: Less costly, fewer QALY gains • Simeprevir plus PR versus boceprevir plus PR: Dominant
Key limitations and CDR estimate(s)	CDR identified a number of issues with the manufacturer's analyses that could have affected the estimates of cost-effectiveness: • There is uncertainty in the comparative SVR rates obtained from the manufacturer-funded NMA, especially in the treatment-experienced populations. • The base case is not representative of the Canadian RGT criteria for simeprevir-PR, telaprevir-PR, and boceprevir-PR. The total costs of treatment with telaprevir-PR and boceprevir-PR were potentially higher than what would be observed in clinical practice. • For treatment-experienced patients, the model assumed that SVR rates would not differ across fibrosis stage, which is inconsistent with the results of clinical trials. • Without boceprevir-PR trial data in previous null responders, the comparative cost-effectiveness of simeprevir-PR and boceprevir-PR in this population is unknown. • Considering the possibility that the prevalence of Q80K polymorphism in Canada might be slightly higher than that observed in clinical trials, if testing for Q80K is not routinely done prior to initiating simeprevir-PR, the ICUR of simeprevir-PR versus its comparators would be increased. • In both treatment-naive and treatment-experienced patients, the ICUR

Drug Product	Simeprevir (Galexos)
	of simeprevir-PR versus PR alone was less than $50,000 per QALY in most scenarios. The ICUR of simeprevir-PR compared with other DAAs varied widely in the sensitivity analyses, which reflects uncertainty surrounding the SVR estimates and price of telaprevir and boceprevir. • CDR performed additional sensitivity analyses: o In treatment-naive patients, when ▪ slightly lower drug costs were used ▪ RGT criteria were based on Canadian label simeprevir-PR dominated telaprevir-PR and resulted in an ICUR of $32,147 per QALY versus boceprevir-PR and $35,489 per QALY versus PR alone. ▪ Further, when a lower 95% CrI for SVR NMA results for simeprevir-PR versus PR were used, simeprevir-PR was dominated by telaprevir-PR. Simeprevir-PR had an ICUR of $1,077,988 per QALY compared with boceprevir-PR, and $45,319 per QALY compared with PR alone. o In treatment-experienced patients, when ▪ slightly lower drug costs were used ▪ RGT criteria were based on Canadian label simeprevir-PR was dominated by telaprevir-PR, simeprevir-PR dominated boceprevir-PR and resulted in an ICUR of $21,240 per QALY versus PR alone. ▪ Further, when lower 95% CrI for SVR NMA results for simeprevir-PR versus PR and upper 95% CrI for SVR NMA results for boceprevir-PR versus PR and telaprevir-PR versus PR were applied (and the efficacy of boceprevir-PR in null responders was assumed similar to telaprevir-PR): simeprevir-PR was dominated by telaprevir-PR and boceprevir-PR and resulted in an ICUR of $47,279 per QALY versus PR alone.

CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; CrI = credible interval; CUA = cost-utility analysis; DAA = direct-acting antiviral agent; ICUR = incremental cost-utility ratio; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SVR = sustained virologic response.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Simeprevir (Galexos) is a protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa plus ribavirin (PR) in adults with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon therapy (pegylated or non-pegylated) with ribavirin.[1] The recommended dose is 150 mg daily for 12 weeks. The total duration of treatment with PR is 24 or 48 weeks, based on HCV RNA levels at treatment week 4.[1]

The manufacturer submitted a non-confidential price of $434.55 per day ($36,503 per 12-week regimen).[2] The manufacturer is requesting listing with similar criteria to other direct-acting antiviral agents (DAAs) used for the treatment of CHC genotype 1 for patients who are naive to antiviral CHC treatment, and for patients who have failed previous interferon therapy.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis (CUA) comparing simeprevir plus PR against telaprevir plus PR, boceprevir plus PR, and PR alone for patients with CHC infection with genotype 1 according to their treatment history: treatment-naive or treatment-experienced. The analysis was based on two phases: a treatment phase (Weeks 0 to 72), and a natural disease progression phase (Weeks 72 to lifetime).

Efficacy data, in terms of sustained virologic response (SVR), were derived from two manufacturer-funded, unpublished, network meta-analyses (NMAs). Treatment-naive and treatment-experienced populations were assessed in separate networks. The cumulative incidence of complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) over a patient's lifetime was forecasted using published rates of progression among individuals with CHC infection. The manufacturer assumed that patients achieving SVR were essentially cured and did not progress to develop complications. The comparative risk of adverse events (AEs) such as anemia, neutropenia, rash, and pruritus was obtained from the NMAs. Treatment-related utility decrements based on changes in EQ-5D scores observed during treatment for simeprevir and its comparators were applied to reflect the decrease in patients' quality of life while on antiviral therapy (48 weeks). During the natural disease progression phase, utility changes were dependent on whether the patient had achieved SVR or whether the disease was progressing. Health state utility values were derived from Chong et al.[3] Costs of the drugs were obtained from BC Pharmacare Formulary. The duration of therapy, which had an impact on drug costs, was weighted by the proportion of patients who qualified to receive a shorter duration of therapy in clinical trials using a response-guided therapy (RGT) regimen. The resource utilization pattern related to the monitoring of patients was based on Canadian guidelines[4,5] and cost was assessed using standard Ontario sources. The costs to manage AEs and HCV and its associated complications were derived from published sources.[6,7]

Results of Manufacturer's Analysis

In treatment-naive patients, the manufacturer reported that simeprevir-PR dominated telaprevir-PR (lower total costs and greater clinical benefits), and that simeprevir-PR resulted in an incremental cost-

utility ratio (ICUR) of $5,202 per QALY and $32,497 per QALY compared with boceprevir-PR and PR alone, respectively.

In treatment-experienced patients, simeprevir-PR was less expensive, but provided fewer QALYs compared with telaprevir-PR. Simeprevir-PR dominated boceprevir-PR, and simeprevir-PR resulted in an ICUR of $20,430 per QALY compared with PR alone.

Interpretations and Key Limitations

CDR identified a number of issues with the manufacturer's analyses that could affect the estimates of cost-effectiveness:

- The cost-effectiveness of simeprevir-PR is largely dependent on the validity of the manufacturer-funded NMAs. There was a lack of detailed information on the methods and analyses used in the NMAs, which complicates proper critical appraisal of the NMA and brings uncertainty to the ICURs, especially in treatment-experienced patients. The manufacturer acknowledged the paucity of data and the high uncertainty around the estimates in treatment-experienced subpopulations.[8]
- The cost of therapies is affected by the proportion of patients eligible to receive a shorter duration of therapy based on RGT criteria. The base-case analysis submitted by the manufacturer assumed that prior relapsers on telaprevir-PR, as well as prior relapsers and partial responders on boceprevir-PR, would not be eligible to receive shorter therapy, which is inconsistent with the Canadian product monograph of these products. Therefore, the base case likely overestimated the total cost of treatment with telaprevir-PR and boceprevir-PR.
- For treatment-experienced patients, the model assumed that SVR rates would not differ across fibrosis stage, which is inconsistent with results from ASPIRE and PROMISE in which the proportion of patients achieving an SVR was generally higher in the F0–F2 group compared with the F3–F4 group.
- Without boceprevir-PR trial data for the null responder population, the comparative cost-effectiveness of simeprevir-PR and boceprevir-PR in that population is unknown.

Results of CDR Analysis

CDR performed additional sensitivity analyses to test the impact of the identified areas of uncertainty:

- In treatment-naive patients, the parameter with the greatest impact on the results was the comparative SVR rate of simeprevir-PR versus PR obtained from the NMA. When the lower bound of the 95% credible interval (CrI) was used, lower drug costs and Canadian label dosing were applied. Simeprevir-PR was dominated by telaprevir-PR, and simeprevir-PR had an ICUR of $1,077,988 per QALY compared with boceprevir-PR and $45,319 per QALY compared with PR alone.
- In treatment-experienced patients, comparative SVR rates obtained from the NMA also had the greatest impact on the results. In a scenario where lower cost for drugs was used, RGT criteria were based on Canadian label, the lower 95% CrI of the SVR NMA results for simeprevir-PR versus PR was applied, and the upper 95% CrI for boceprevir-PR versus PR and telaprevir-PR versus PR was applied (the efficacy of boceprevir-PR in null responders was assumed to be similar to telaprevir-PR), simeprevir-PR was dominated by telaprevir-PR and boceprevir-PR and resulted in an ICUR of $47,279 per QALY versus PR alone.

Issues for Consideration

- Costs and resources required for the testing for the Q80K polymorphism were not included in the analysis. Of note, in its comments on the CDR draft reports, the manufacturer indicated that it will pay for all costs associated with logistics, testing, and reporting of Q80K polymorphism. Testing for the Q80K polymorphism is currently available through the BC Centre for Excellence Research Laboratory. Janssen's agreement with the BC Laboratory ensures that clinicians and patients across Canada (except Quebec) have access to the test through coordination with provincial public health labs. The results will be sent back to the public health lab and ultimately to the requesting physician, indicating whether the Q80K polymorphism is present or absent. The turnaround time is approximately 14 days.

Conclusions

In both treatment-naive and treatment-experienced patients, the ICUR of simeprevir-PR versus PR alone was less than $50,000 per QALY in most scenarios performed by CDR. The ICUR of simeprevir-PR compared with other DAA-PR regimens varied widely in sensitivity analyses performed by CDR, which reflects uncertainty surrounding the SVR estimates obtained from the NMA especially in the treatment-experienced population. Based on CDR reanalysis in which lower drug costs and Canadian label dosing were applied, simeprevir-PR dominated telaprevir-PR and led to an ICUR of $32,147 per QALY versus boceprevir-PR and $35,489 per QALY versus PR alone in treatment-naive patients. In treatment-experienced patients, simeprevir-PR was dominated by telaprevir-PR (greater total costs and reduced clinical benefits). Simeprevir-PR dominated boceprevir-PR and led to an ICUR of $21,240 per QALY versus PR alone.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"From the perspective of the provincial Ministry of Health, what is the incremental cost-effectiveness of simeprevir in treatment of CHC infection compared with boceprevir and telaprevir, and compared with standard therapy with peginterferon and ribavirin?"[9]

1.2 Treatment

Simeprevir 150 mg daily for 12 weeks in combination with peginterferon alfa plus ribavirin (PR) for 24 or 48 weeks

1.3 Comparators

- Telaprevir in combination with PR
- Boceprevir in combination with PR
- PR alone

Sofosbuvir in combination with PR was not included as a comparator, as it had not been reviewed by CDR at the time of this submission, nor was it listed by any of the public drug plans.

1.4 Type of Economic Evaluation

A cost-utility analysis (CUA) was undertaken and is appropriate according to the CADTH guidelines. The perspective was that of the Ministry of Health.

Further to the findings of the CUA, the manufacturer performed a cost-minimization (CMA) analysis, which has been summarized in Appendix 3 of this report. Considering the uncertainty surrounding the NMA results, especially in treatment-experienced patients, the CUA submitted by the manufacturer was used as the basis of the CDR pharmacoeconomic (PE) report, as it allowed a better exploration of uncertainty through sensitivity analyses. CMA does not appear to be an appropriate choice of economic evaluation. Indeed, the validity of a CMA is contingent on establishing similar efficacy and safety. However, in prior relapsers, the manufacturer-conducted NMA showed that patients treated with simeprevir-PR were [redacted].[10]

1.5 Population

The population for the economic analysis consisted of CHC genotype 1 treatment-naive or treatment-experienced patients considered to be suitable candidates for simeprevir therapy. The baseline characteristics of the patients included in the model were extracted from the QUEST-1 study.[11] The mean age at baseline was 46.1 years and 56.3% were males.

The assumed fibrosis stages for treatment-naive and treatment-experienced patients are presented in Table 2.

TABLE 2: ASSUMED DISTRIBUTION OF DISEASE SEVERITY AT BASELINE

Fibrosis stage	Treatment-naive (%)	Treatment-experienced (%)	Source
F0–F2 Mild chronic HCV	68.0	50.5	Hartwell,[12] ERG report for boceprevir[13]
F3 Moderate chronic HCV	22.0	17.5	Hartwell,[12] ERG report for boceprevir[13]
F4 Compensated cirrhosis	10.0	32.0	Hartwell,[12] ERG report for boceprevir[13]

ERG = Evidence Review Group; HCV = hepatitis C virus.

In treatment-experienced patients, distribution between prior relapsers, partial responders, and null responders was taken from the ASPIRE trial,[14] and was as follows:

- Prior relapsers: 39.4%
- Partial responders: 34.8%
- Null responders: 25.8%

The population used in the model reflects the Health Canada indication for simeprevir.[1]

2. METHODS

Please see Table 18 for the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

The analysis was based on two phases: a treatment phase (weeks 0 to 72) and a natural disease progression phase (weeks 72 to lifetime). For the treatment phase, a decision-tree model was used; the model used ORs obtained from the NMA for SVR and incidence of treatment-related AEs. For the natural disease progression phase, a Markov model was used to model long-term outcomes.

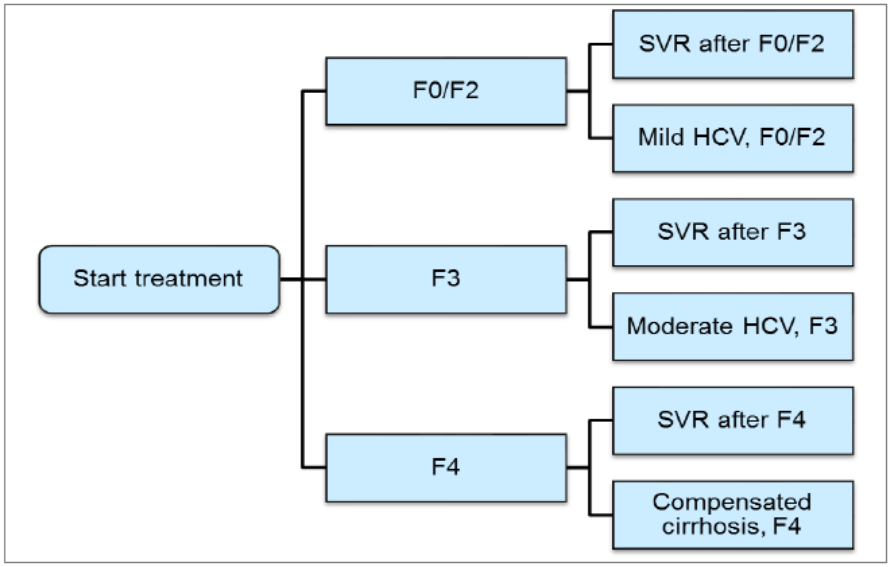
2.1.1 Treatment Phase

At baseline, patients with genotype 1 CHC enter the model according to their stage of liver fibrosis as determined by their METAVIR score, and initiate dual (PR) or triple antiviral drug therapy (DAA plus PR).

During the first 48 weeks, patients receive the assigned treatment regimen from the clinical trial protocol, and may or may not experience AEs. At the end of therapy:

- Patients with detectable hepatitis C virus ribonucleic acid (HCV RNA) are considered treatment failures and will remain in their original CHC health state (determined by their METAVIR score at baseline).
- Patients with undetectable HCV RNA are followed for 24 weeks. After 24 weeks, if patients still have undetectable HCV RNA, they are considered to have an SVR (SVR24), or to be cured of the viral infection.
- If patients have detectable HCV RNA at the 24-week follow-up point, they are considered to have a relapse and they remain in their original CHC health state (determined by their METAVIR score at baseline).

FIGURE 1: DECISION-TREE USED FOR THE TREATMENT PHASE (WEEKS 0 TO 72)



HCV = hepatitis C virus; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[9]

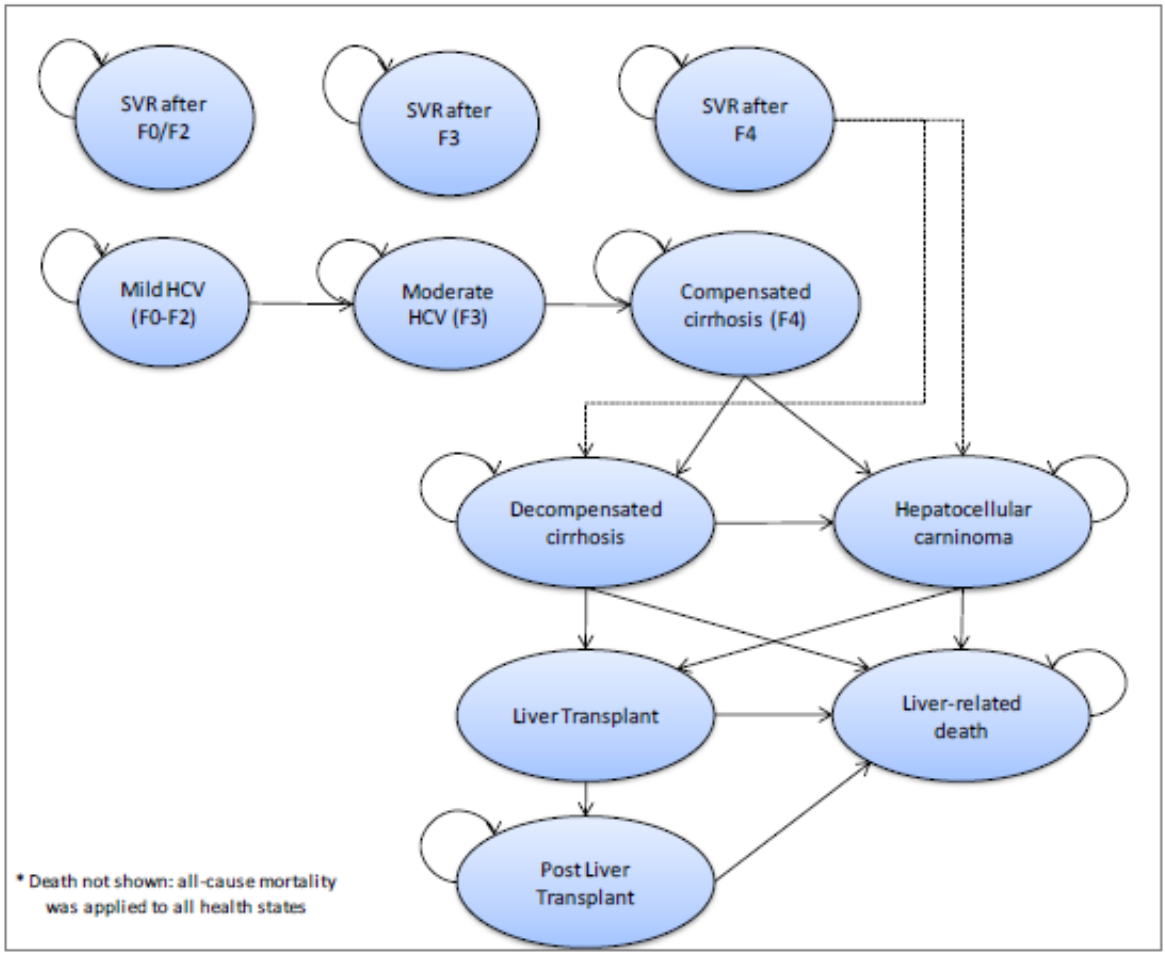
2.1.2 Natural Disease Progression Phase

The long-term clinical outcomes are extrapolated with a Markov model incorporating the natural disease progression of CHC. The model includes 11 health states (see Figure 2). All-cause mortality was applied to all health states. The cycle length was 1 year. After the initial 72-week treatment phase, patients in each fibrosis state are assumed to have either achieved SVR or to have failed therapy.

Patients achieving an SVR following treatment are assumed to be free of future liver complications, although compensated cirrhotic patients who achieve an SVR are still at risk of developing decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC).

Without successful treatment, patients with mild CHC, moderate CHC, or compensated cirrhosis (F4) may remain in their current health state or progress to more severe stages of liver disease.

FIGURE 2: MARKOV MODEL USED FOR THE NATURAL DISEASE PROGRESSION (WEEKS 72 TO LIFETIME)



HCV = hepatitis C virus; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[9]

2.2 Clinical Inputs

2.2.1 Efficacy

Without head-to-head trials comparing the efficacy and safety of DAA-PR regimens, manufacturer-funded unpublished NMAs were conducted using standard 48-week PR dual therapy as a common comparator group for treatment-naive and treatment-experienced patients. A summary and critical appraisal of the NMAs submitted by the manufacturer is presented in Appendix 6 of the CDR Clinical Review.

Results from the NMA that were used to inform the economic model are presented in Table 3. In treatment-naive patients, the NMA showed no significant difference between the three DAA-PR combinations for the SVR rates.

In treatment-experienced patients, the NMA showed no significant difference between the three DAA-PR combinations for the SVR rates for prior partial responders (likely due to sparse evidence in the network) and null responders (boceprevir was not included in the network). [redacted]

[redacted].[10]

TABLE 3: NMA RESULTS FOR SVR USED IN THE MODEL: ODDS RATIOS OF ACHIEVING SVR WITH DAA PLUS PR TREATMENT REGIMENS VERSUS PR48

	Treatment-naive OR (95% CrI)	Prior Relapsers OR (95% CrI)	Partial Responders OR (95% CrI)	Null Responders OR (95% CrI)
SIM-PR versus PR48				
SIM12PR24/48	3.77 (2.80 to 5.09)	[redacted]	[redacted]	[redacted]
SIM12PR48	---	[redacted]	[redacted]	[redacted]
TEL-PR versus PR48				
TEL12PR24/48	3.80 (2.79 to 5.23)	[redacted]	[redacted]	[redacted]
TEL12PR48	---	[redacted]	[redacted]	[redacted]
BOC-PR – RGT versus PR48				
BOC24PR28/48	2.98 (2.23 to 4.01)	[redacted]	[redacted]	[redacted]
BOC32PR36/48	---	[redacted]	[redacted]	[redacted]
BOC-PR – FIX versus PR48				
BOC44PR48	3.53 (2.70 to 4.64)	[redacted]	[redacted]	[redacted]
Probability of achieving SVR in the PR arm				
PR F0/F2 Probability	0.51 (0.36 to 0.67)	[redacted]	[redacted]	[redacted]
PR F3/F4 Probability	0.39 (0.25 to 0.59)	[redacted]	[redacted]	[redacted]

BOC = boceprevir; CrI = credible interval; DAA = direct-acting antiviral; FIX = fixed-treatment regimen; OR = odds ratio; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SIM = simeprevir; SVR = sustained virologic response; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submisison[9] and additional information submitted per CADTH request.[8]

For treatment-naive patients, the ORs from the NMA were applied to the probability of achieving SVR with PR48 therapy. The latter data were obtained from a baseline Bayesian model using the PR arms of five randomized controlled trials included in the NMA that presented the results stratified by METAVIR F0/F2 and F3/F4 (ADVANCE, SPRINT-225, PILLAR, QUEST-1, and QUEST-2). As presented in Table 4, the proportion of patients achieving an SVR was generally higher in the F0–F2 group compared with the F3–F4 group.

For treatment-experienced patients, the ORs from the NMA presented in Table 3 were applied to the probability of achieving SVR with PR48 therapy from the REALIZE[15] clinical trial. Following a request from CDR to justify why a baseline model was not used, the manufacturer indicated that only results from REALIZE were used "because of the small number of patients and the absence of extensive data on these subpopulations and therefore high uncertainty around the estimates."[8] The model assumed that SVR rates would not differ across fibrosis stage, which is inconsistent with results from ASPIRE and PROMISE, in which, similar to treatment-naive patients, the proportion of patients achieving an SVR was

generally higher in the F0–F2 group compared with those in the F3–F4 group (Table 4). None of the boceprevir trials in treatment-experienced patients included prior null responders. The manufacturer assumed that the SVR rate would be the same as for simeprevir-PR.

TABLE 4: SVR RATES USED IN THE MANUFACTURER'S MODEL FOR SIMEPREVIR-PR AND COMPARATORS BY FIBROSIS STAGE AND POPULATION TYPE BASED ON THE ODDS RATIO OBTAINED FROM NMA

	Naive	Relapse	Partials	Null
SIM-PR				
SVR rate F0/F2	79.7%	[redacted]	[redacted]	[redacted]
SVR rate F3	70.6%	[redacted]	[redacted]	[redacted]
SVR rate F4	70.6%	[redacted]	[redacted]	[redacted]
TEL-PR				
SVR rate F0/F2	79.8%	[redacted]	[redacted]	[redacted]
SVR rate F3	70.8%	[redacted]	[redacted]	[redacted]
SVR rate F4	70.8%	[redacted]	[redacted]	[redacted]
BOC-PR – RGT				
SVR rate F0/F2	75.7%	[redacted]	[redacted]	[redacted]
SVR rate F3	65.6%	[redacted]	[redacted]	[redacted]
SVR rate F4	65.6%	[redacted]	[redacted]	[redacted]
BOC-PR – FIX				
SVR rate F0/F2	78.7%	[redacted]	[redacted]	[redacted]
SVR rate F3	69.3%	[redacted]	[redacted]	[redacted]
SVR rate F4	69.3%	[redacted]	[redacted]	[redacted]
PR				
SVR rate F0/F2	51.1%	[redacted]	[redacted]	[redacted]
SVR rate F3	38.9%	[redacted]	[redacted]	[redacted]
SVR rate F4	38.9%	[redacted]	[redacted]	[redacted]

BOC = boceprevir; FIX = fixed-treatment regimen; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SIM = simeprevir; SVR = sustained virologic response; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

2.2.2 Treatment Duration

The average treatment duration was based on the proportion of patients fulfilling the criteria for RGT, which was directly extracted from the simeprevir, telaprevir, and boceprevir phase III clinical trials (Table 5). In the case of telaprevir clinical trials, RGT was not tested in the REALIZE clinical trial. Therefore, the model assumed that with telaprevir, treatment-experienced patients were not eligible for shorter treatment duration.

TABLE 5: PROPORTION OF PATIENTS MEETING CRITERIA FOR SHORTER TREATMENT DURATION (RGT) AND MEAN DURATION OF TREATMENT APPLIED IN THE MODEL

	Proportion of Patients Meeting RGT Criteria (%)	Average Treatment Duration (Weeks)	Data Source
SIM-PR			
Treatment-naive	87.7	SIM: 12.00 PR: 26.96	Average from QUEST-1 and QUEST-2
Treatment-experienced	92.7 (prior relapsers)	SIM: 12.00 PR: 42.61	PROMISE
TEL-PR			
Treatment-naive	58.4	TEL: 12.00 PR: 33.98	ADVANCE[16]
Treatment-experienced	0[a]	TEL: 12.00 PR: 48.00	REALIZE[15]
BOC24-PR28/48 – RGT			
Treatment-naive	44.0	BOC: 26.00 PR: 40.08	SPRINT-2[17]
BOC44-PR48 – FIX			
Treatment-experienced[b]	0	BOC: 44.00 PR: 48.00	Assumption
PR48			
Treatment-naive	0	48.00	
Treatment-experienced	0	48.00	

BOC = boceprevir; FIX = fixed-treatment regimen; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SIM = simeprevir; TEL = telaprevir.
[a] Although in the Canadian product monograph for telaprevir, prior relapsers are eligible for RGT therapy.
[b] Although in the Canadian product monograph for boceprevir, prior relapsers and partial responders are eligible for RGT therapy (except F4 patients).
Source: Manufacturer's pharmacoeconomic submission.[9]

2.2.3 Harms

AEs included in the model were anemia, neutropenia, rash, and pruritus. The ORs obtained from the NMA were applied to the baseline probability of experiencing each AE with PR therapy to determine the probabilities of experiencing an AE for each DAA treatment. The source used to obtain the baseline probability in the PR arm was not described in the manufacturer's submission (Table 6). Costs associated with the treatment of AEs were applied, but there was no disutility applied to the patients experiencing AEs.

TABLE 6: ADVERSE EVENTS RATES USED IN THE HEALTH ECONOMICS MODEL

	Anemia		Neutropenia		Rash		Pruritus	
	Treatment - naive (%)	Treatment-experienced (%)	Treatment-naive (%)	Treatment-experienced (%)	Treatment - naive (%)	Treatment-experienced (%)	Treatment-naive (%)	Treatment-experienced (%)
SIM-PR	20.0	13.7	22.6	19.3	26.9	15.2	33.1	31.2
TEL-PR	44.0	37.1	14.2	19.6	36.4	29.4	42.8	42.6
BOC-PR – RGT	43.0	34.9	18.5	24.5	39.6	42.1	38.6	22.2
BOC-PR – FIX	42.9	36.1	20.2	24.5	37.9	37.0	41.0	23.1
PR	29.9	20.8	19.0	14.9	24.1	14.4	29.9	20.8

BOC = boceprevir; FIX = fixed-treatment regimen; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SIM = simeprevir; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

As shown in Table 6, anemia was the AE for which the incidence was significantly lower with simeprevir compared with all other comparators.

2.2.4 Disease Progression/Transition Probabilities

The model assumes that patients who become HCV-negative and who have F4 fibrosis stage (i.e., SVRF4) can still progress to more severe health states — [DCC] and [HCC]), as it is not assumed that being cured of the viral infection eradicates existing liver damage.

TABLE 7: TRANSITION PROBABILITIES USED IN THE ECONOMIC MODEL

From	To	Value	Source
F0-F2	F3	0.041	CADTH[18]
F3	F4	0.124	Krahn et al.[19]
F4	DCC	0.046	Krahn et al.[19]
	HCC	0.021	Krahn et al.[19]
SVR F4	DCC	0.008	Ferrante et al.[20]
	HCC	0.006	CADTH[18]
DCC	HCC LT Liver-related death	0.014 0.033 0.138	Hartwell et al.;[12] Fattovitch et al.[21] CADTH[18]/Krahn et al.[19] Krahn et al.[19]
HCC	LT	0.031	El Saadany et al.[22]
	Liver-related death	0.860	CADTH[18]/Krahn et al.[19]
LT	Liver-related death	0.169	CADTH[18]/Krahn et al.[19]
pLT	Liver-related death	0.034	CADTH[18]/Krahn et al. .[19]

DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LT = liver transplant; pLT = post-liver transplant; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[9]

2.2.5 Mortality

All-cause mortality was obtained from age- and sex-specific *Life Tables for Canada 2007–2009* (Statistics Canada).

The model assumed that individuals in the mild chronic HCV, moderate chronic HCV, compensated cirrhosis, and the three corresponding SVR health states, do not experience excess mortality. Patients with DCC, HCC, liver transplantation (LT) or post-liver transplant (pLT) may die from liver-related causes. The probability of liver-related death in DCC (0.138), HCC (0.860), LT (0.169) and pLT (0.034) were taken from previous Canadian economic evaluations.[18,19]

To reflect higher mortality rates in the year immediately following LT compared with later years, the LT health state had to be divided into two distinct states: The LT health state lasts for a total of one year. If alive at the end of the year, the patient transitions to the post-liver transplant (pLT) health state, experiencing a decreased mortality risk.

2.2.6 Costs

Resource use was considered from the perspective of the Ministry of Health.

2.2.7 Drug Costs

The cost of simeprevir was obtained from the manufacturer ($434.55 per day; $36,502.55 per 12-week regimen).

Other drug costs were based on unit prices listed on the BC Pharmacare Formulary. Of note, the BC Pharmacare Formulary includes a markup.

For PR, the model assumed that 50% of patients receive peginterferon alfa, and 50% receive peginterferon beta.

2.2.8 Monitoring Costs

Events involved in monitoring CHC patients receiving a protease inhibitor plus PR therapy (e.g., HCV viral load) were defined by reviewing Canadian guidelines. The resource utilization pattern was then assessed for cost using standard Ontario sources, and the monitoring costs for PR and each protease inhibitor plus PR therapy were determined.

2.2.9 Adverse Event Costs

Costs related to the management of anemia, rash, pruritus, and neutropenia were based on a budget impact analysis by Thorlund et al.,[6] done in the United Kingdom setting. Resource utilization and treatment patterns related to the management of AEs were obtained from interviews with pharmacies and clinical experts. This resource pattern was then assessed for cost using unit costs from Ontario. According to the clinical expert consulted for this review, the resource utilization pattern was similar to that observed in Canadian practice, but the expert noted that the proportion of anemic patients requiring erythropoietin therapy might be lower than 20%.

TABLE 8: COST OF ADVERSE EVENTS

Adverse event	Resource utilization pattern	Cost of event $C
Anemia	Hematology consultation plus one repeat Erythropoietin therapy (20% of patients) Blood transfusion (5% of patients)	440.27
Neutropenia	Hematology consultation plus full blood count	165.27
Rash	Dermatologist consultation Hydrocortisone gel	80.31
Pruritus	Dermatologist consultation Hydroxyzine 25 mg capsules	86.40

Source: Thorlund et al.[6]

2.2.10 Health State Costs

The majority of costs were obtained from the CADTH 2007 evaluation.[18] DCC costs were obtained from Krahn et al.[19] and updated to 2012. The model incorporates a cost for health states F0/F2, F3 and F4 after SVR has been achieved, based on the premise that these patients still incur treatment costs; costs for SVR F0/F2 and F3 apply only for one year after treatment, but the costs for SVR F4 apply for five years. However, costs for these SVR health states could not be obtained from the Canadian sources. Instead, costs for these health states were derived from health technology assessments (HTAs) on the treatment of HCV in the United Kingdom-based mainly on data from an HCV trial in the United Kingdom.

2.2.11 Utilities

a) Treatment Phase

Treatment-related utility decrements were applied to reflect the decrease in the health-related quality of life that patients experience while on antiviral therapy. The model assumes that these utility decrements apply for the 48 weeks during treatment. After week 48, the model assumes that patient utility returns to the baseline value and remains there until week 72 (Table 9). Utility decrements for telaprevir (from ADVANCE and REALIZE) and simeprevir (from PILLAR and ASPIRE) were obtained by comparing the baseline (Day 1) EQ-5D score with the average EQ-5D captured during the year of treatment (Weeks 4 to 48). For boceprevir, patient-level data were not available, so the average utility

decrement was estimated based on mean values reported at weeks 8, 12, 24, and 48 for patients receiving boceprevir plus PR and PR alone (Table 9).

TABLE 9: SUMMARY OF UTILITY DECREMENT APPLIED DURING THERAPY FOR TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS IN THE MANUFACTURER'S BASE-CASE ANALYSIS

	Treatment-naive				Treatment-experienced			
	SIM	TEL	BOC	PR	SIM	TEL	BOC	PR
Utility decrement	–0.059	–0.104	RGT: –0.094 FIX: –0.109	–0.111	–0.113	–0.161	RGT: –0.109 FIX: –0.120	–0.133

BOC = boceprevir; FIX = fixed-treatment regimen; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy; SIM = simeprevir; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

Utility changes beyond week 72 were dependent on whether the patient had achieved SVR or if disease was progressing. Based on Chong et al.,[3] the base-case analysis assumed that the utility gain with SVR was 0.04.

b) Natural Disease Progression Phase:
Health state utilities were obtained from a Canadian study by Chong et al.[3] The utilities of 193 CHC patients (N = 193) were assessed using a visual analogue scale, standard gamble, the Health Utilities Index Mark 3 (HUI Mark 3) survey, and the EuroQol 5-Dimensions scale (EQ-5D). Of note, no patients were undergoing treatment at the time of the interview. The HUI Mark 3 utilities were used in the model in line with previous Canadian models. Chong et al. found no statistically significant differences between utility values for different health states, possibly because of the small sample size; they commented that across the clinical spectrum of HCV, changes in quality of life were not large.

2.2.12 Time Horizon
The model used a lifetime horizon (~68 years). According to the manufacturer's PE submission, a lifetime horizon is necessary to capture all the essential consequences of the disease, since serious complications of CHC may not be apparent for decades following the initial infection.

This time horizon is consistent with other economic models of hepatitis C that were developed by HTA agencies.[12,18]

2.2.13 Discounting
Both outcomes and costs accrued beyond the first year of the model were discounted at a rate of 5%, as per the CADTH guidelines.

2.2.14 Validation
The model validation process is described in the manufacturer's PE submission:[9] the model was duplicated in TreeAge to test for Excel modelling calculation errors. The manufacturer performed several tests to check if the model ran correctly and produced accurate results.

3. RESULTS

3.1 Manufacturer's Base Case

3.1.1 Overall SVR Rates and Cumulative Incidences of Severe Liver Disease

TABLE 10: MANUFACTURER'S FORECASTED CUMULATIVE INCIDENCE OF LIVER COMPLICATIONS OVER LIFETIME IN PATIENTS WHO ARE TREATMENT-NAIVE OR TREATMENT-EXPERIENCED

Outcome	SIM-PR (%)	TEL-PR (%)	BOC-PR RGT (%)	PR (%)
Treatment-naive				
SVR	76.69	76.89	72.66	47.09
DCC	10.73	10.66	12.18	21.17
HCC	6.06	6.02	6.78	11.29
LT	1.86	1.85	2.11	3.63
LrD	13.54	13.45	15.27	25.97
Treatment-experienced				
SVR	54.83	56.92	52.67	13.08
DCC	23.24	22.49	24.02	38.19
HCC	13.30	12.95	13.66	20.26
LT	4.10	3.97	4.24	6.70
LrD	29.90	29.01	30.82	47.65

DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SIM = simeprevir; PR = peginterferon alfa plus ribavirin; TEL = telaprevir; BOC = boceprevir; RGT = response-guided therapy; LT = liver transplant; LrD = liver-related death.
Source: Manufacturer's pharmacoeconomic submission.[9]

3.1.2 Incremental Cost per QALY

a) Treatment-Naive

In the reference case, the manufacturer reported that simeprevir-PR dominated telaprevir-PR. Compared with boceprevir-PR and dual therapy with PR, the incremental cost per QALY gained with simeprevir-PR was $5,202 and $32,497, respectively (Table 11).

b) Treatment-Experienced

In the reference case, the manufacturer reported that, compared with telaprevir-PR, treatment with simeprevir-PR resulted in lower costs (–$2,440) but a slight QALY loss (–0.003). Simeprevir-PR dominated boceprevir-PR and resulted in an incremental cost per QALY gained of $24,877 compared with dual therapy with PR (Table 11).

TABLE 11: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (DISCOUNTED)

	Total Costs ($)	Incremental Cost of Simeprevir ($)	Total QALYs	Incremental QALYs of Simeprevir	Incremental Cost per QALY: SIM vs. Comparator ($)
Treatment-naive					
SIM-PR	58,080	---	12.23	---	---
TEL-PR	61,738	–3,658	12.19	0.037	Dominant
BOC-PR	57,485	595	12.11	0.114	5,202
PR	37,789	20,291	11.60	0.624	32,497
Treatment-experienced					
SIM-PR	73,944	---	11.34	---	---
TEL-PR	76,384	–3,888	11.34	–0.020	Less expensive, fewer QALY gains
BOC-PR	89,118	–16,790	11.29	0.054	Dominant
PR	49,853	21,563	10.37	1.055	20,430

BOC = boceprevir; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; RGT = response-guided therapy; SIM = simeprevir; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

3.2 Summary of the Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic and probabilistic sensitivity analyses.

3.2.1 Deterministic Sensitivity Analyses

Model parameters were varied separately within the limits of their 95% confidence intervals (CI). In cases where 95% CI were not available, values were varied over a 20% range.

Deterministic sensitivity analyses in treatment-naive patients are shown in Table 12. The ICUR of SIM-PR compared with boceprevir-PR was shown to be highly sensitive to the SVR rate of simeprevir compared with PR alone. Using the lower bound of the 95% CrI resulted in an ICUR of $390,603 per QALY.

Deterministic sensitivity analyses in treatment-experienced patients are shown in (Table 13).

TABLE 12: MANUFACTURER'S SENSITIVITY ANALYSES IN TREATMENT-NAIVE PATIENTS

Comparison	Scenario	ICUR ($/QALY) for SIM-PR
SIM-PR vs. TEL-PR	All	SIM-PR was dominant or less costly and fewer QALY gains
SIM-PR vs. BOC-PR	Lower 95% CrI for SVR OR of SIM12-PR24/48 vs. PR48 (OR = 2.82)	390,603
	Upper 95% CrI for SVR OR of BOC24PR28/48 vs. PR48 (OR = 4.01):	156,175
	Shortened time horizon to antiviral therapy phase (72 weeks) and 30 years	42,323 to 7,638
SIM-PR vs. PR	Lower 95% CrI for the SVR OR of SIM12-PR24/48 vs. PR48 (OR = 2.82)	41,688
	Variation of fibrosis distribution (F0-F2: 80%, F3: 10%, F4: 10%)	38,008
	Shortened time horizon to antiviral therapy phase (72 weeks) and 30 years	550,505 to 45,067

BOC = boceprevir; ICUR = incremental cost-utility ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir; TEL = telaprevir; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[9]

TABLE 13: MANUFACTURER'S SENSITIVITY ANALYSES IN TREATMENT-EXPERIENCED PATIENTS

Comparison	Scenario	ICUR ($/QALY) for SIM-PR
SIM-PR vs. TEL-PR	Majority of scenarios	Less costly, fewer QALY gains
	Lower 95% CrI for the SVR OR of TEL vs. PR	Dominant
	Upper 95% CrI for the SVR OR of SIM vs. PR	Dominant
	Shortened time horizon to antiviral therapy phase (72 weeks) and 30 years	Less costly, fewer QALY gains
SIM-PR vs. BOC-PR	Majority of scenarios	Dominant
	Shortened time horizon to antiviral therapy phase (72 weeks) and 30 years	Dominant
	Lower 95% CrI for the SVR, Relapsers (SIM vs. PR): OR = 4.31	Less costly, fewer QALY gains
	Upper 95% CrI for the SVR, Relapsers (BOC vs. PR): OR = 11.62	Less costly, fewer QALY gains
	Lower 95% CrI for the SVR, partial responders, (SIM vs. PR): OR = 5.13	Less costly, fewer QALY gains
	Treatment utility decrement: SIM/PR (–0.060)	Less costly, fewer QALY gains
SIM-PR vs. PR	Lower 95% CrI for the SVR OR of SIM12-PR48 vs. PR48 in partial responders: OR = 5.13	31,510
	Lower 95% CrI PR (partial responders)	25,090
	Transition probability from F4 to DCC (0.03)	24,667
	Shortened time horizon to antiviral therapy phase (72 weeks) and 30 years	1,722,865 and 27,908

BOC = boceprevir; CrI = credible interval; DCC = decompensated cirrhosis; ICUR = incremental cost-utility ratio; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir; TEL = telaprevir; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[9]

3.2.2 Probabilistic Sensitivity Analysis

Simulations were processed to represent the uncertainty of model results by varying the parameters by random draws from their assumed distributions. For the outputs of the NMA, 1,000 simulations were directly extracted from the WinBugs code. Based on the simulations, a scatterplot and an acceptability curve were drawn to estimate the probability of simeprevir being considered cost-effective against its comparator treatments at a given willingness-to-pay (WTP) threshold per QALY gained.

a) Treatment-Naive

According to the acceptability curves from the probabilistic sensitivity analyses, there is a 71% probability that the ICUR would fall below a $35,000 per QALY threshold compared with telaprevir-PR, boceprevir-PR, and PR alone.

b) Treatment-Experienced:

At a WTP threshold of $30,000, the probability of simeprevir being cost-effective for treatment-experienced genotype 1 HCV patients compared with telaprevir-PR, boceprevir-PR, and PR alone is approximately 62%.

3.3 CADTH Common Drug Review Analyses

CDR reviewers performed several additional sensitivity analyses in both treatment-naive (Table 14) and treatment-experienced patients (Table 15). First, Ontario Drug Benefit Exceptional Access Program and Saskatchewan Drug Benefit costs, instead of BC Pharmacare costs, were applied (lower costs). Second, RGT criteria based on the Canadian label instead of clinical trials were applied as these were considered to better represent current Canadian practice. These resulted in a lower percentage of patients receiving shorter therapy with simeprevir-PR (75% instead of 88% in treatment-naive patients, 76% instead of 90% in prior relapsers), and a greater proportion of prior relapsers receiving shorter therapy with telaprevir-PR (65.5% instead of 0%) and boceprevir-PR (45.7% instead of 0%).

Furthermore, given the wide CrIs around the NMA results, uncertainty in prevalence of Q80K polymorphism in Canadian patients and the small number of studies in the network, especially in treatment-experienced patients, sensitivity analyses were performed in which the lower bound of the 95% CrI SVR OR for the simeprevir-PR versus PR comparison was applied (treatment-naive and treatment-experienced patients), and the upper bound of the 95% CrI SVR OR for the telaprevir-PR versus PR and boceprevir-PR versus PR comparisons were applied (treatment-experienced patients only).

TABLE 14: CDR REANALYSIS FOR SIMEPREVIR-PR VERSUS COMPARATORS IN TREATMENT-NAIVE PATIENTS

Comparator	Incremental Cost of SIM-PR ($)	Incremental QALYs of SIM-PR	ICUR for SIM-PR ($/QALY)
Scenario A: Using ODB Exceptional Access Program and SK Drug Benefit costs (see Appendix 1) instead of BC PharmaCare costs			
TEL-PR	–1,764	0.037	Dominant
BOC-PR	2,241	0.114	19,599
PR	20,725	0.624	33,191
Scenario B: Scenario A plus Proportion of patients meeting RGT criteria based on Canadian label instead of clinical trials			
TEL-PR	–975	0.037	Dominant
BOC-PR	3,676	0.114	32,147
PR	22,160	0.624	35,489
Scenario C: Scenario B plus lower 95% CrI for SVR OR of SIM-PR vs. PR (OR = 2.82)			
TEL-PR	185	–0.073	Dominated
BOC-PR	4,835	0.004	1,077,988
PR	33,319	0.515	45 319

BC = British Columbia; BOC = boceprevir; CDR = CADTH Common Drug Review; CrI = credible interval; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; RGT = response-guided therapy; SIM = simeprevir; SK = Saskatchewan; TEL = telaprevir.

TABLE 15: CDR REANALYSIS FOR SIMEPREVIR-PR VERSUS COMPARATORS IN TREATMENT-EXPERIENCED PATIENTS

Comparator	Incremental Cost of SIM-PR ($)	Incremental QALYs of SIM-PR	ICUR for SIM-PR vs. Comparator ($/QALY)
Scenario A: Using ODB Exceptional Access Program and SK Drug Benefit costs (see Appendix 1) instead of BC Pharmacare costs			
TEL-PR	–1959	–0.020	Less costly, fewer QALY gains
BOC-PR	–14,281	0.054	Dominant
PR	21,744	1.055	20,601
Scenario B: Scenario A plus Proportion of patients meeting RGT criteria based on Canadian label instead of clinical trials			
TEL-PR	655	–0.020	Dominated
BOC-PR	–5,971	0.054	Dominant
PR	22,418	1.055	21,240
Scenario C: Scenario B plus SVR BOC null responders = SVR TEL instead of SIM			
TEL-PR	655	–0.020	Dominated
BOC-PR	–5,148	–0.026	Less costly, fewer QALY gains
PR	22,418	1.055	21,240
Scenario D: Scenario C plus lower 95% CrI for SVR OR of SIM-PR vs. PR			
TEL-PR	5,587	–0.497	Dominated
BOC-PR	–216	–0.503	Less costly, fewer QALY gains
PR	27,350	0.578	47,279
Scenario E: Scenario D plus upper 95% CrI for BOC-PR vs. PR and TEL-PR vs. PR			
TEL-PR	11,067	–1.027	Dominated
BOC-PR	4,905	–1.000	Dominated
PR	27,350	0.578	47,279

BC = British Columbia; BOC = boceprevir; CDR = CADTH Common Drug Review; CrI = credible interval; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; RGT = response-guided therapy; SIM = simeprevir; SK = Saskatchewan; TEL = telaprevir; vs. = versus.
Note: The manufacturer did not provide ICURs per specific treatment-experienced population. In an attempt to assess the variability across type of prior response, CDR performed an additional sensitivity analysis in which 100% of patients were assumed to be prior relapsers, partial responders, or null responders, respectively (Table 16).

TABLE 16: CDR REANALYSIS FOR TREATMENT-EXPERIENCED PATIENTS BASED ON PRIOR RESPONSE TO PR

Comparator	Incremental cost of simeprevir ($)	Incremental QALYs of simeprevir	ICUR ($/QALY)
Scenario B from Table 15			
Assuming treatment-experienced patients are 100% prior relapsers			
TEL-PR	2,958	–0.380	Dominated
BOC-PR	–7,909	–0.005	Less costly, fewer QALY gains
PR	17,653	1.015	17,396
Assuming treatment-experienced patients are 100% partial responders			
TEL-PR	–3,987	0.568	Dominant
BOC-PR	–1,011	0.155	Dominant
PR	20,612	1.557	13,242
Assuming treatment-experienced patients are 100% null responders			
TEL-PR	4,629	–0.266	Dominated
BOC-PR	–6,512	–0.304	Less costly, fewer QALY gains
PR	32,159	0.440	73,109

BC = British Columbia; BOC = boceprevir; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; SK = Saskatchewan; SIM = simeprevir; TEL = telaprevir.

Considering that CDR noted areas of uncertainty in the ICURs for both treatment-naive and treatment-experienced patients, the potential impact of a simeprevir price reduction was explored (Table 17).

Furthermore, telaprevir and boceprevir received positive listing recommendations from the CADTH Canadian Drug Expert Committee (CDEC) conditional on a reduced price. Therefore, scenarios in which prices of the two drugs were reduced by 10 and 15% were also explored. (Table 17).

TABLE 17: CDR ANALYSIS OF ICURS BASED ON VARIOUS PRICE REDUCTION SCENARIOS

Scenario/ comparator	Treatment-naive Revised ICUR SIM-PR vs. comparator Based on "ODB/SK costs and Canadian Label dosing" Scenario B from Table 14 ($/QALY)	Treatment-experienced Revised ICUR SIM-PR vs. comparator Based on CDR "ODB/SK costs and Canadian Label dosing" Scenario B from Table 15 ($/QALY)
Simeprevir price reduction scenarios		
Submitted price ($434.55)		
TEL-PR	Dominant	Dominated
BOC-PR	32,147	Dominant
PR	35,489	21,240
10% price reduction ($391.10)		
TEL-PR	Dominant	Less costly, fewer QALY gains
BOC-PR	230	Dominant
PR	29,245	17,782
20% price reduction ($347.64)		
TEL-PR	Dominant	Less costly, fewer QALY gains
BOC-PR	Dominant	Dominant
PR	23,798	14,323
30% price reduction ($304.09)		
TEL-PR	Dominant	Less costly, fewer QALY gains
BOC-PR	Dominant	Dominant
PR	17,953	10,857
50% price reduction ($217.28)		
TEL-PR	Dominant	Less costly, fewer QALY gains
BOC-PR	Dominant	Less costly, fewer QALY gains
PR	6,395	3,948
Telaprevir and Boceprevir price reduction scenarios		
10% price reduction (TEL: $62.443/unit, BOC: $11.25/unit)		
TEL-PR	67,582	Dominated
BOC-PR	56,023	Dominant
PR	35,489	21,240
15% price reduction (TEL: $58.974/unit, BOC: $10.625/unit)		
TEL-PR	114,444	Dominated
BOC-PR	67,960	97
PR	35,489	21,240

BOC = boceprevir; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir; SK = Saskatchewan Drug Benefit; TEL = telaprevir; vs. = versus.

The CDR reanalysis shows that ICURs are sensitive to the price reductions of simeprevir, telaprevir, or boceprevir.

4. DISCUSSION

The manufacturer submitted a CUA comparing simeprevir-PR to telaprevir-PR, boceprevir-PR, and PR alone for patients with CHC infection with genotype 1 according to their treatment history: treatment-naive or treatment-experienced. The analysis was based on two phases: a treatment phase (Weeks 0 to 72), and a natural disease progression phase (weeks 72 to lifetime).

Comparative SVR and specific AE rates (for anemia, rash, pruritus, and neutropenia) were derived from the manufacturer-funded, unpublished NMA. As noted by the manufacturer, ICURs were very sensitive to SVR rates obtained through the NMAs. There was a lack of detailed information on the methods and analyses used in the NMA, especially for those performed in treatment-experienced patients and for AEs. Further to a request for clarification from CDR, the manufacturer acknowledged [redacted].

For treatment-experienced patients, the model assumed that SVR rates would not differ across fibrosis stage, which is inconsistent with the results from ASPIRE and PROMISE in which the proportion of patients achieving an SVR was generally higher in the F0–F2 group compared with the F3–F4 groups.

Other limitations were identified that raise uncertainty surrounding the ICURs estimated by the manufacturer, especially in the treatment-experienced population. The cost of therapies is affected by the proportion of patients eligible to receive a shorter duration of therapy, based on RGT criteria. The base-case analysis submitted by the manufacturer assumed that no telaprevir prior relapsers or boceprevir prior relapsers, or partial responders would receive shorter therapy, which is inconsistent with the Canadian product monograph of these products and which overestimated the cost of the telaprevir-PR and boceprevir-PR regimens that would be expected in clinical practice. In addition, the base-case analysis used the proportion of patients who received shorter therapy in QUEST-1 and QUEST-2 (88%). However, the Canadian label is slightly different from the clinical program: RGT criteria are met only if HCV RNA is undetectable (< 15 IU/mL instead of < 25 IU/mL in clinical trials). Using the Canadian label RGT criteria, 75% of treatment-naive and prior-relapse patients qualified for RGT with simeprevir-PR.

Without boceprevir-PR trial data for the null responder population, the values from simeprevir-PR were imputed to make the assumption of no difference between the therapies. This brings a lot of uncertainty to the results for that population. A more conservative approach would have been to impute the results from telaprevir-PR, in which a greater proportion of patients achieving SVR was observed.

Treatment-related utility decrements applied for 48 weeks during the treatment phase were based on EQ-5D scores obtained from different clinical trials, and were not adjusted for baseline utility. Furthermore, changes in EQ-5D scores observed in clinical trials might be different from those observed in clinical practice. As an example, prior relapsers with telaprevir might have shown greater utility decrements in clinical trials than they would have in clinical practice considering that RGT is recommended in these patients, which is likely to result in a smaller incidence of side effects. Furthermore, the fact that some of the trials did not allow for the use of erythropoietin in patients with severe anemia might also have resulted in greater utility decrements than are observed in clinical practice.

The key limitations associated with the manufacturer's submission are summarized in Table 18.

TABLE 18: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Proportion of patients eligible to receive shorter duration of therapy, based on RGT criteria.	Base case is not representative of Canadian RGT criteria for SIM-PR, TEL-PR, and BOC-PR.	Underestimation of the cost of therapy with SIM-PR in treatment-naive and prior relapsers; Overestimation of the cost of therapy with TEL-PR and BOC-PR in prior relapsers.
NMA results reflect comparative SVR rates of agents in treatment-experienced patients.	The number of trials included in the network is small; No data were provided by the manufacturer on how stratification by type of prior response was done; The CrI are very wide; Baseline PR SVR rates were obtained from only one TEL trial (REALIZE).	Uncertainty in the NMA results; SVR rates in the SIM-PR obtained by applying ORs from NMA to PR SVR rates from REALIZE might have been overestimated.
In treatment-experienced patients, SVR rates are not affected by fibrosis stage.	This is not consistent with the results of ASPIRE, in which patients with fibrosis stage F3-F4 showed lower rates of SVR compared with patients with fibrosis stage F1-F2.	Uncertain.
Without BOC-PR trial data for the null responder population, the values from SIM-PR were imputed to make the conservative assumption of no difference between the therapies.	A more conservative approach would have been to impute the results from TEL-PR.	The comparative cost-effectiveness of SIM-PR and BOC-PR in that population is unknown. The manufacturer's assumption might have underestimated the efficacy of BOC-PR in that population.
Treatment-related utility decrement are smaller with SIM-PR compared with TEL-PR and BOC-PR.	The model applies utility decrements taken from different clinical trials without adjusting for potential differences in baseline utility score.	Overestimation of the difference in utility decrements between DAA agents; Potential overestimation of incremental QALY gains with SIM-PR.

BOC = boceprevir; DAA = direct-acting antiviral; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; OR = odds ratio; PR = peginterferon alfa plus ribavirin; QALY = quality-adjusted life-year; SIM = simeprevir; SVR = sustained virologic response; TEL = telaprevir.

4.1 Issues for Consideration

The impact of Q80K polymorphism on SVR rates with simeprevir-PR was not assessed in the economic analysis. SVR rates of simeprevir-PR (including the proportion of subjects meeting RGT criteria) were reduced in genotype 1a patients with Q80K polymorphism at baseline compared with those without Q80K polymorphism. In phase IIb and phase III studies of simeprevir, the prevalence of Q80K polymorphism in patients with HCV genotype 1a in North America was 48% compared with 30% in the overall population included in the studies.[1]

The product monograph indicates that testing for Q80K polymorphism could be considered when clinicians consider initiating simeprevir-PR therapy. Costs and resources required for that test were not included in the analysis. Of note, in their comments on the CDR draft reports, the manufacturer indicated that it will pay for all costs associated with logistics, testing, and reporting of Q80K

polymorphism. Janssen's agreement with the BC Laboratory ensures that clinicians and patients across Canada have access to the test through coordination with provincial public health labs. (Quebec-based clinicians can access testing through the Laboratoire Public Santé du Quebec.) Clinicians can submit a requisition form to their provincial lab to request Q80K polymorphism sequencing, which directs the blood sample to the BC Centre for Excellence Research Laboratory for analysis. The results will be sent back to the public health lab and ultimately to the requesting physician, indicating whether the Q80K polymorphism is present or absent. Other potentially relevant polymorphisms in the NS3 region will also be reported. The turnaround time is approximately 14 days.

Considering that the prevalence of Q80K polymorphism in Canada might be slightly higher than that observed in clinical trials, if testing for Q80K is not routinely done prior to initiating simeprevir-PR, the ICUR of simeprevir-PR versus its comparators would be increased, given that lower SVR rates would likely be observed.

4.2 Patient Input

Patient input was received from five patient groups: the Canadian Liver Foundation, Canadian Treatment Action Council, Hepatitis C Education and Prevention Society, Pacific Hepatitis C Network's mission, and the Gastrointestinal Society. The patient input highlights that one of simeprevir's potential advantages over boceprevir and telaprevir would be its effectiveness in harder-to-treat patients such as those who have failed peginterferon-ribavirin treatment. Of note, in prior relapsers, the NMA showed no difference between simeprevir-PR and boceprevir-PR, but patients treated with simeprevir-PR were [redacted].[10] Furthermore, the lack of clinical trial data in prior null responders with boceprevir limits potential comparisons in this population.

Patient input noted the potential for decreased AEs with simeprevir compared with boceprevir and telaprevir. Although some differences, such as lower risk of anemia, were noted in the NMA submitted by the manufacturer favouring simeprevir compared with boceprevir and telaprevir, severity of anemia was not considered in the NMA. As noted by the manufacturer, the cost and incidence of AEs were not found to have a significant impact on the incremental cost per QALY estimates.

5. CONCLUSIONS

In both treatment-naive and treatment-experienced patients, the ICUR of simeprevir-PR versus PR alone was less than $50,000 per QALY in most scenarios reported by the manufacturer and performed by CDR. The ICUR of simeprevir-PR compared with other DAA-PR regimens varied widely in the sensitivity analyses performed by CDR, which reflects uncertainty surrounding the SVR estimates obtained from the NMA, especially in the treatment-experienced population. Based on the CDR reanalysis in which lower drug costs and Canadian label dosing were applied, simeprevir-PR dominated telaprevir-PR, and led to an ICUR of $32,147 per QALY versus boceprevir-PR and $35,489 per QALY versus PR alone in treatment-naive patients. In treatment-experienced patients, simeprevir-PR was dominated by telaprevir-PR (greater total costs and reduced clinical benefits). Simeprevir-PR dominated boceprevir-PR and led to an ICUR of $21,240 per QALY versus PR alone.

APPENDIX 1: COST COMPARISON TABLE

Clinical experts have deemed the comparators presented in Table 19 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 19: COST COMPARISON TABLE FOR DRUGS FOR CHRONIC HEPATITIS C, GENOTYPE 1

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)
Simeprevir (Galexos)	150 mg	Cap	434.5500[a]	150 mg daily	12 weeks	36,502
HCV Protease Inhibitor						
Boceprevir (Victrelis)	200 mg	Cap	12.5000	4 × 200 mg 3 times daily	24 to 44 weeks	25,200 to 46,200
Telaprevir (Incivek)	375 mg	Tab	69.3810	3 × 375 mg 2 times daily	12 weeks	34,968
Nucleotide Analogue NS5B Polymerase Inhibitor						
Sofosbuvir (Sovaldi)	400 mg	Tab	710.4168[b]	400 mg once daily	12 weeks	59,675
Combination PegIFN Alfa Plus RBV Therapy						
PegIFN alfa-2a plus RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe/ 28 Tabs	395.8400[c]	PegIFN 180 mcg/week; RBV 800 mg/day to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000
PegIFN alfa-2b plus RBV (Pegetron)	50 mcg/200 mg	2 vials plus 56 caps	774.7700[c]	PegIFN 1.5 mcg/kg/week; RBV 800 mg/day to 1,400 mg/day[d]	24 to 48 weeks	9,297 to 18,594
	150 mcg/200 mg	2 vials plus 84 or 98 caps	856.1200[c]			10,273 to 20,547
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	774.7700[c] 774.7700[c] 856.1200[c] 856.1200[c]			9,297 to 20,547
Combination Boceprevir Plus Peginterferon Alfa Plus RBV Therapy						
Boceprevir, PegIFN alfa-2a plus RBV (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 caps plus 2 pens plus 56 caps	2652.55 2652.55 2726.00 2726.00	Boceprevir 800 mg 3 times daily; PegIFN 1.5 mcg/kg/week; RBV 800 mg/day to 1,400 mg/day[d]	24 to 44 weeks	31,831 to 59,972

IFN = interferon; IM = intramuscular; IU = international unit; IV = intravenous; M = millions; PegIFN = peginterferon; RBV = ribavirin.

[a] Manufacturer's submitted price.

[b] McKesson Canada (April 2014). Includes markup.

[c] Saskatchewan Drug Benefit (April 2014).

[d] Dosing varies by weight and HCV genotype.

Source: Ontario Drug Benefit Exceptional Access Program (April 2014) prices unless otherwise stated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 20: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SIMEPREVIR-PR RELATIVE TO PR?

Simeprevir-PR Vs. PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Treatment-naive						
Costs (total)				X		
Drug treatment costs alone					X	
Clinical Outcomes	X					
Quality of life		X				
Incremental CE ratio or net benefit calculation	$35,489/QALY					
Treatment-experienced						
Costs (total)				X		
Drug treatment costs alone					X	
Clinical Outcomes	X					
Quality of life		X				
Incremental CE ratio or net benefit calculation	$21,240/QALY					

CE = cost-effectiveness; NA = not applicable; PR = peginterferon alfa plus ribavirin.
Note: Table 20 is based on CADTH Common Drug Review reanalysis scenario B (OPDP/Saskatchewan drug costs plus proportion of patients meeting response-guided therapy criteria based on Canadian label).

TABLE 21: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SIMEPREVIR-PR RELATIVE TO TELAPREVIR-PR?

Simeprevir-PR Vs. Telaprevir-PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Treatment-naive						
Costs (total)		X				
Drug treatment costs alone		X				
Clinical Outcomes			X			
Quality of life		X				
Incremental CE ratio or net benefit calculation	Simeprevir-PR dominates telaprevir-PR					
Treatment-experienced						
Costs (total)				X		
Drug treatment costs alone			X			
Clinical Outcomes				X		
Quality of life				X		
Incremental CE ratio or net benefit calculation	Simeprevir-PR is dominated by telaprevir-PR					

CE = cost-effectiveness; NA = not applicable; PR = peginterferon alfa plus ribavirin.
Note: Table 21 is based on CADTH Common Drug Review reanalysis Scenario B (OPDP/Saskatchewan drug costs plus proportion of patients meeting response-guided therapy criteria based on Canadian label).

TABLE 22: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SIMEPREVIR-PR RELATIVE TO BOCEPREVIR-PR?

Simeprevir-PR Vs. Boceprevir-PR	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Treatment-naive						
Costs (total)				X		
Drug treatment costs alone				X		
Clinical Outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$32,147/QALY					
Treatment-experienced						
Costs (total)		X				
Drug treatment costs alone		X				
Clinical Outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Simeprevir dominates boceprevir-PR					

CE = cost-effectiveness; NA = not applicable; PR = peginterferon alfa plus ribavirin.
Note: Table 22 is based on CADTH Common Drug Review reanalysis Scenario B (OPDP/Saskatchewan drug costs plus proportion of patients meeting response-guided therapy criteria based on Canadian label).

APPENDIX 3: SUMMARY OF COST-MINIMIZATION ANALYSIS

The manufacturer submitted a cost-minimization analysis (CMA) comparing simeprevir in combination with peginterferon alfa plus ribavirin (PR) to telaprevir in combination with PR and boceprevir in combination with PR in treatment-naive and treatment-experienced patients with genotype 1 chromic hepatitis C (CHC).[9] The choice of a simeprevir was based on the results of a network meta-analysis (NMA), which showed that sustained virologic response (SVR) rates did not differ significantly between the three direct-acting antiviral (DAA) agents for treatment-naive or treatment-experienced patients. The manufacturer considered the CMA as a conservative analysis, as it did not consider the potential lower risk of treatment-related adverse events (AEs) with simeprevir-PR compared with other DAAs.[9]

Only drug costs were considered. Unit costs were obtained from BC Pharmacare. Costs were calculated for the duration of a treatment regimen, based on a 12-week regimen for simeprevir and telaprevir, and on 24, 32, and 44-week regimens for boceprevir.

The average costs of treatment for treatment-naive and prior relapser were determined by using the proportion of patients in the clinical studies that met response-guided therapy (RGT) criteria (based on Canadian label) to weight the duration of PR dual therapy.

TABLE 23: MANUFACTURER'S CMA BASE-CASE SCENARIO FOR TREATMENT-NAIVE PATIENTS

Drug / Comparator	Proportion of Patients Meeting RGT Criteria	Triple Therapy Duration (Weeks)	Average Duration of PR Therapy (Weeks)	Cost Triple Therapy ($)	Cost Dual Therapy ($)	Total Cost ($)
Simeprevir (label-based)	0.75	12	18[a]	41,489.78	7,481.38	48,971.16
Telaprevir	0.58	12	22.08	41,703.98	9,177.15	50,881.14
Boceprevir	0.44	24	37.44	36,445.25	15,561.26	52,006.51
Boceprevir (F4)	NA	44	4	66,816.29	1,662.53	68,478.82

CMA = cost-minimization analysis; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy.
[a] Average length of dual therapy = (0.75 × 12) plus (0.25 × 36) = 18.
Source: Manufacturer's pharmacoeconomic submission.[9]

TABLE 24: MANUFACTURER'S CMA BASE-CASE SCENARIO FOR PRIOR RELAPSER PATIENTS

Drug / Comparator	Proportion of Patients Meeting RGT Criteria	Triple Therapy Duration (Weeks)	Average Duration of PR Therapy (Weeks)	Cost Triple Therapy ($)	Cost Dual Therapy ($)	Total Cost ($)
Simeprevir (label-based)	0.77	12	17.52	41,489.78	7,281.87	48,771.66
Telaprevir	0.76	12	17.76	41,703.98	7,381.62	49,085.61
Boceprevir	0.46	32	36.96	48,593.66	15,361.76	63,955.42

CMA = cost-minimization analysis; PR = peginterferon alfa plus ribavirin; RGT = response-guided therapy.
Source: Manufacturer's pharmacoeconomic submission.[9]

For treatment-experienced patients that did not qualify for RGT (null or partial responders, or prior relapsers that did not meet RGT criteria), the costs of treatment were similar. The cost of simeprevir treatment including PR was $56,453 compared with $56,667 for telaprevir and $55,244 for boceprevir.

In summary, the manufacturer reported that in treatment-naive patients, simeprevir-PR would result in savings of $1,910 compared with telaprevir-PR, and savings ranging from $3,035 to $19,508 compared with boceprevir-PR. In prior relapsers, simeprevir-PR would result in savings of $314 compared with telaprevir-PR, and savings of $15,184 compared with boceprevir-PR. In null responders, partial responders, or prior relapsers that do not meet RGT criteria, simeprevir-PR would result in savings of $214 compared with telaprevir-PR, but would result in an incremental cost of $1,209 compared with boceprevir-PR.

Key Limitations

- **Assumption of similar efficacy and potentially better safety profile with simeprevir-PR versus telaprevir-PR and boceprevir-PR based on results of NMAs:** Limitations of the NMA results for SVR rates and safety outcomes have been summarized in Appendix 6 of the CDR clinical report. A degree of uncertainty remains about the efficacy and safety of simeprevir-PR compared with those of telaprevir-PR and boceprevir-PR, especially in the treatment-experienced population. (The validity of a CMA is contingent on establishing similar efficacy and safety). In prior relapsers, the NMA showed no difference between simeprevir-PR and boceprevir-PR, but patients treated with simeprevir-PR [redacted].[10] Furthermore, without boceprevir-PR trial data for the null responder population, the comparative cost-effectiveness of simeprevir-PR and boceprevir-PR in this population is unknown.
- **Costs associated with testing for Q80K polymorphism was not considered:** Of note, in its comments on the CDR draft reports, the manufacturer indicated that it will pay for all costs associated with logistics, testing, and reporting of Q80K polymorphism. Janssen's agreement with the BC Laboratory ensures that clinicians and patients across Canada have access to the test through coordination with provincial public health labs. (Quebec-based clinicians can access testing through the Laboratoire Public Santé du Quebec.) Clinicians can submit a requisition form to their provincial lab to request Q80K polymorphism sequencing, which directs the blood sample to the BC Centre for Excellence Research Laboratory for analysis. The manufacturer indicated that the test would be available through the BC Centre for Excellence Research Laboratory [redacted].[23] The manufacturer noted that it would cover the costs of testing all samples through the BC Laboratory. Of note, the test is also available in Quebec, but is not covered by the manufacturer. As stated in the simeprevir product monograph,[1] when accessible, testing for Q80K polymorphism in patients with HCV genotype 1a could be considered.
- **Proportion of patients meeting RGT criteria with simeprevir**: The CMA submitted by the manufacturer assumes that the percentage of patients meeting RGT criteria with simeprevir in the Canadian clinical setting will be similar to that observed in clinical trials (adjusted for the Canadian label). The CMA did not consider the potentially greater prevalence of Q80K polymorphism in the North American population compared with the overall prevalence observed in clinical trials. As noted in the product monograph, in phase IIb and phase III studies of simeprevir, the prevalence of Q80K polymorphism in patients with HCV genotype 1a in North America was 48% compared with 30% in the overall population included in the studies. In simeprevir trials, treatment-naive and treatment-experienced patients with Q80K polymorphism had lower rates of rapid virologic response at week 4 compared with patients without polymorphism. Therefore, there is a possibility

that the percentage of patients meeting RGT criteria might be lower, which would reduce the differential cost of simeprevir with that of telaprevir and boceprevir.

Summary of Findings

Results of the CMA conducted by the manufacturer suggest that simeprevir-PR regimen costs are generally comparable to the costs of regimens with telaprevir-PR and boceprevir-PR. When the duration of treatment is weighted by proportion of patients who qualified for RGT, simeprevir is found to be the least costly alternative for treatment-naive and prior relapser patients. However, the proportion of patients who qualified for RGT in the clinical program might differ from that observed in clinical practice, especially if the prevalence of Q80K in the Canadian population differs from that of the overall population included in the trials, and if Q80K is not routinely done prior to initiating simeprevir-PR therapy.

Given the uncertainty and conflicting results from the NMA, [redacted], CMA does not appear to be an appropriate choice of economic evaluation. Indeed, the validity of a CMA is contingent on establishing similar efficacy and safety. However, in prior relapsers, the manufacturer-conducted NMA showed that patients treated with simeprevir-PR were [redacted].[10] Without boceprevir-PR trial data in the null responder population, the comparative cost-effectiveness of simeprevir-PR and boceprevir-PR in this population is unknown.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 25: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 26: AUTHOR INFORMATION

Authors	Affiliations
Canadian model adaptation: John McCormick	McKesson Canada

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

REFERENCES

1. [Pr]Galexos™ (simeprevir capsules): 150 mg simeprevir (as simeprevir sodium) [product monograph]. Toronto: Janssen Inc.; 2013 Nov 18.
2. CDR submission: simeprevir 150 mg capsules. Company: Janssen Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto: Janssen Inc.; 2013 Aug.
3. 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.
4. Sherman M, Shafran S, Burak K, Doucette K, Wong W, Girgrah N, et al. Management of chronic hepatitis C: consensus guidelines. Can J Gastroenterol [Internet]. 2007 Jun [cited 2014 Jan 14];21 Suppl C:25C-34C. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2794457
5. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of chronic hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2014 Feb 14];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284/
6. Thorlund K, Druyts E, El Khoury AC, Mills EJ. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. Clinicoecon Outcomes Res [Internet]. 2012 [cited 2014 Jan 23];4:349-59. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503472/pdf/ceor-4-349.pdf
7. 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. Appendices 1-4 [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007 Mar. [cited 2014 Feb 3]. (Technology report no 82). Available from: http://www.cadth.ca/media/pdf/232_Hep-C_tr_appendices_e.pdf
8. Janssen Inc. response to February 7, 2014 CDR request for additional information regarding the Galexos CDR review: part 2 **[CONFIDENTIAL** additional manufacturer's information]. Toronto: Janssen Inc.; 2014 Feb 19.
9. Pharmacoeconomic evaluation. In: CDR submission: simeprevir 150 mg capsules. Company: Janssen Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto: Janssen Inc.; 2013 Aug.
10. Janssen Inc. response to February 7, 2014 CDR request for additional information regarding the Galexos CDR review: part 3 **[CONFIDENTIAL** additional manufacturer's information]. Toronto: Janssen Inc.; 2014 Feb 24.
11. Clinical study report: TMC435-TiDP16-C208 (QUEST-1). A phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon alfa-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects [**CONFIDENTIAL** internal manufacturer's report]. [Raritan (NJ)]: Janssen Research & Development; 2013 Feb 12.
12. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess [Internet]. 2011 Apr [cited 2014 Feb 3];15(17):i-210. Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0017/65312/FullReport-hta15170.pdf

13. Mendes D, White K, Cooper K, Bryant J. Boceprevir for the treatment of genotype 1 chronic hepatitis C [Internet]. Southampton, United Kingdom: Southampton Health Technology Assessments Centre; 2011. [cited 2014 Feb 28]. (Evidence review group report commissioned by the NHS R&D HTA Programme on behalf of NICE). Available from: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0008/82583/ERGReport-10-149-01.pdf

14. Clinical study report: TMC435-TiDP16-C206. A phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNalfa-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNalfa-2a/b and RBV therapy [**CONFIDENTIAL** internal manufacturer's report]. [Raritan (NJ)]: Janssen Research & Development; 2012 Jul 4.

15. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

16. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med [Internet]. 2011 Jun 23 [cited 2014 Jan 16];364(25):2405-16. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1012912

17. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

18. 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: Canadian Agency for Drugs and Technologies in Health; 2007 Mar. [cited 2014 Feb 3]. (Technology report no 82). Available from: http://www.cadth.ca/media/pdf/232_HepC_tr_e.pdf

19. Krahn MD, John-Baptiste A, Yi Q, Doria A, Remis RS, Ritvo P, et al. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. Vaccine. 2005 Feb 18;23(13):1549-58.

20. 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 Apr 27 [cited 2014 Mar 19];13(1):190. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643851

21. 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.

22. El Saadany S, Coyle D, Giulivi A, Afzal M. Economic burden of hepatitis C in Canada and the potential impact of prevention. Results from a disease model. Eur J Health Econ. 2005 Jun;6(2):159-65.

23. Janssen Inc. response to February 7, 2014 CDR request for additional information regarding the Galexos CDR review: part 1 **[CONFIDENTIAL** additional manufacturer's information]. Toronto: Janssen Inc.; 2014 Feb 18.