Common Drug Review
Pharmacoeconomic Review Report

October 2014

Drug	Sofosbuvir (Sovaldi) (400 mg/tablet)
Indication	Sofosbuvir is indicated for the treatment of chronic hepatitis C virus (CHC) infection in adult patients with compensated liver disease, including cirrhosis, as follows: • For the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon and ribavirin (Peg-INF/RBV); • For the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin.
Listing request	Gilead is requesting that sofosbuvir receive a positive listing recommendation for the treatment of patients with CHC, based on the following criteria: • treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection • Peg-INF/RBV-experienced patients with chronic HCV genotype 2 infection • Peg-INF/RBV-experienced patients with chronic HCV genotype 3 infection; and • genotype 2 and 3 CHC patients for whom interferon is medically contraindicated.
Manufacturer	Gilead Sciences Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the 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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TABLE OF CONTENTS

Figures

ABBREVIATIONS

AE	adverse event
BOC	boceprevir
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CrI	credible interval
CUA	cost-utility analysis
DAA	direct-acting antiviral
DCC	decompensated cirrhosis
EASL	European Association for the Study of the Liver
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HUI	health utility index
INF	interferon
LT	liver transplant
NMA	network meta-analysis
OR	odds ratio
Peg-INF/RBV	pegylated interferon plus ribavirin
QALY	quality-adjusted life-year
RGT	response-guided therapy
SOF	sofosbuvir
SVR	sustained virologic response
TEL	telaprevir

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Sofosbuvir (Sovaldi)
Study Question	What is the incremental cost-effectiveness of sofosbuvir versus appropriate comparators, over a lifetime horizon and from a government perspective, in patients with all genotypes of CHC infection? Detailed analyses focused on the patient subgroups identified in the reimbursement request (see target population).
Type of Economic Evaluation	CUA
Target Population	• TN patients with CHC G1 infection • TE patients with CHC G2 infection • TE patients with CHC G3 infection • G2 and G3 CHC patients for whom INF is medically contraindicated
Treatment	G1 TN: sofosbuvir+Peg-INF/RBV x 12 wks G2: sofosbuvir+RBV x 12 wks G3: sofosbuvir+RBV x 16 wks
Outcomes	Cost per LY gained; Cost per QALY gained
Comparators	• G1 TN: Peg-INF/RBV for 48 wks, TEL for 12 wks +Peg-INF/RBV for 24-48 wks, BOC for 24-44 wks + Peg-INF/RBV 28-48 wks • G2: No treatment, Peg-INF/RBV48 (TE non-responders, relapse, breakthrough) • G3: No treatment, Peg-INF/RBV48 (TE non-responders, relapse, breakthrough)
Perspective	Publicly funded health care system
Time Horizon	Lifetime (up to 100 years of age)
Manufacturer's Results (Base Case)	**G1 TN:** • Non-cirrhotic: sofosbuvir vs. Peg-INF/RBV: $31,323/QALY, sofosbuvir vs. TEL: $5,076/QALY; sofosbuvir vs. BOC: $15,599/QALY; • Cirrhotic: sofosbuvir vs. Peg-INF/RBV: $1,197/QALY; sofosbuvir vs. TEL: sofosbuvir is dominant; sofosbuvir vs. BOC: sofosbuvir is dominant **G2 TN INF-ineligible:** • Non-cirrhotic: sofosbuvir vs. no treatment: $19,614/QALY • Cirrhotic: sofosbuvir vs. no treatment: $ 40/QALY **G2 TE INF-intolerant:** • Non-cirrhotic: sofosbuvir vs. no treatment: $17,765/QALY • Cirrhotic: sofosbuvir vs. no treatment: sofosbuvir is dominant **G2 TE non-responder:** • Non-cirrhotic: sofosbuvir vs. no treatment: $21,509/QALY, sofosbuvir vs. Peg-INF/RBV: $16,446/QALY • Cirrhotic: sofosbuvir vs. no treatment: sofosbuvir is dominated; sofosbuvir vs. Peg-INF/RBV: sofosbuvir is dominated **G2 TE relapse or breakthrough:** • Non-cirrhotic: sofosbuvir vs. no treatment: $17,765/QALY, sofosbuvir vs. Peg-INF/RBV: $12,323/QALY

	• Cirrhotic: sofosbuvir vs. no treatment: $2,999 /QALY; sofosbuvir vs. Peg-INF/RBV: sofosbuvir is dominant **G3 TN INF-ineligible:** • Non-cirrhotic: sofosbuvir vs. no treatment: $41,935/QALY • Cirrhotic: sofosbuvir vs. no treatment: $52,125/QALY **G3 TE INF-intolerant:** • Non-cirrhotic: sofosbuvir vs. no treatment: $24,536/QALY • Cirrhotic: sofosbuvir vs. no treatment: $58,571 /QALY **G3 TE non-responder:** • Non-cirrhotic: sofosbuvir vs. no treatment: $50,346/QALY, sofosbuvir vs. Peg-INF/RBV: $62,393/QALY • Cirrhotic: sofosbuvir vs. no treatment: $23,709 /QALY; sofosbuvir vs. Peg-INF/RBV: $22,652/QALY **G3 TE relapse or breakthrough:** • Non-cirrhotic: sofosbuvir vs. no treatment: $44,831/QALY; sofosbuvir vs. Peg-INF/RBV: $51,519/QALY • Cirrhotic: sofosbuvir vs. no treatment: $9,573/QALY; sofosbuvir vs. Peg-INF/RBV: $5,777/QALY
Key Limitations and CDR Estimate(s)	CDR identified a number of limitations with the manufacturer's analyses: • The design of NEUTRINO and FUSION required use of historical controls and naive indirect comparisons, which generates uncertainty in the ICURs • Many of the comparisons were based on very small sample sizes and results in some subgroups were not consistent with overall findings from FUSION and POSITRON; e.g., cirrhotic patients presenting better SVR rates than non-cirrhotic patients • Findings from the VALENCE study suggest that G3 patients may benefit from a longer duration of sofosbuvir+ribavirin (up to 24 weeks). Potential longer duration of therapy in these patients was not considered in the model. CDR performed additional sensitivity analyses: • Based on NMA primary analysis results (for G1 non-cirrhotic patients only) • Using conservative SVR rates • Using lower utility values for patients achieving SVR • Using lower treatment costs for anemia. ICURs of sofosbuvir vs. comparators varied widely across genotypes and subgroups: • In G1 TN non-cirrhotic patients, using SVR estimates obtained from the NMA, the ICUR for sofosbuvir vs. Peg-INF/RBV, telaprevir, and boceprevir was $50,266 per QALY, $11,531 per QALY, and $14,030 per QALY, respectively. In a scenario using conservative SVR rates, the ICUR for sofosbuvir vs. Peg-INF/RBV was $135,391 per QALY, and sofosbuvir was dominated by telaprevir and boceprevir. In cirrhotic patients, sofosbuvir generally appeared cost-effective compared with boceprevir and Peg-INF/RBV, but analyses were based on very small subgroups and on a naive indirect treatment comparison. • In G2 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir vs. no treatment remained attractive, in both non-cirrhotic and cirrhotic patients ($28,983 and $3,268 per QALY, respectively). In G2 prior-relapsers, sofosbuvir was generally cost-effective vs. no treatment and vs. Peg-INF/RBV (ICURs ranging from $23,944 to $31,487 per QALY), except vs. Peg-INF/RBV in cirrhotic patients ($62,162 per QALY). In G2 prior non-responders, sofosbuvir was less attractive when compared with no treatment or Peg-INF/RBV in non-cirrhotic and cirrhotic patients (ICURs > $60,000 per QALY, or dominated).

[redacted]	• In G3 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir vs. no treatment were above $75,000 per QALY, in both non-cirrhotic and cirrhotic patients. In G3 prior-relapsers, sofosbuvir was not cost-effective (either dominated or ICURs > $150,000 per QALY) vs. no treatment and vs. Peg-INF/RBV in non-cirrhotic patients, but ICURs were below $31,000 per QALY in cirrhotic patients. In prior non-responders, compared with no treatment and Peg-INF/RBV, sofosbuvir was either dominated, or had ICURs above $150,000 per QALY.

BOC = boceprevir; CDR = Common Drug Review; CHC = chronic hepatitis C; CUA = cost-utility analysis; G = genotype; ICUR = incremental cost-utility ratio; INF = interferon; LY = life-year; NMA = network meta-analysis; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive; wks= weeks

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Sofosbuvir (Sovaldi) is a nucleotide analogue NS5B polymerase inhibitor for the treatment of chronic hepatitis C (CHC). It is indicated for the treatment of CHC virus infection in adult patients with compensated liver disease, including cirrhosis, as follows:

- for the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon plus ribavirin (Peg-INF/RBV);
- for the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin (RBV).[1]

The duration of treatment varies by genotype:[1]

- **Genotype 1 or 4 treatment-naive:** 12 weeks in combination with Peg-INF/RBV
- **Genotype 2:** 12 weeks in combination with RBV
- **Genotype 3:** 16 weeks in combination with RBV. The product monograph indicates that consideration should be given to extending the duration of therapy beyond 16 weeks and up to 24 weeks, guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history).

The manufacturer submitted a confidential price of [redacted] per day, which corresponds to a total cost per course of treatment of [redacted], [redacted], and [redacted] per 12, 16, and 24-week regimen, respectively. The manufacturer is requesting listing for the treatment of patients with CHC based on the following criteria:

- Treatment-naive patients with CHC genotype 1 infection;
- Peg-INF/RBV-experienced patients with CHC genotype 2 infection;
- Peg-INF/RBV-experienced patients with CHC genotype 3 infection;
- Genotype 2 and 3 CHC patients for whom interferon (INF) is medically contraindicated.

The manufacturer did not include treatment-naive patients with genotype 2 and 3 eligible for INF in the reimbursement request, or treatment-naive patients with genotype 4, as sofosbuvir was either dominated or not attractive (ICURs > $90,000 per quality-adjusted life-year [QALY]) in these populations, based on the manufacturer's base-case analysis. The Common Drug Review (CDR) pharmacoeconomic report will focus on the subgroups that were listed in the reimbursement request.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis with a lifetime horizon. The base-case analysis consisted of 24 subgroups (genotype; cirrhosis stage; treatment-naive; treatment-experienced; INF-ineligible, unwilling, or intolerant) generating 36 comparative ICURs. In genotype 1 treatment-naive patients, sofosbuvir in combination with Peg-INF/RBV for 12 weeks was compared with telaprevir plus Peg-INF/RBV, boceprevir plus Peg-INF/RBV, and Peg-INF/RBV. In genotype 2 patients, sofosbuvir in combination with RBV for 12 weeks was compared with Peg-INF/RBV or no treatment. In genotype 3 patients, sofosbuvir in combination with RBV for 16 weeks was compared with Peg-INF/RBV or no treatment.

For efficacy data, in genotype 1 patients, without a comparator group in NEUTRINO, for the base-case analysis, sustained virologic response (SVR) rates were chosen from the intervention group of the pivotal trials for telaprevir and boceprevir (SPRINT-2 and ADVANCE) and from IDEAL for Peg-INF/RBV (naive indirect treatment comparison). In a sensitivity analysis, comparative SVR rates from a manufacturer-funded, unpublished network meta-analysis (NMA) in non-cirrhotic patients were used.[2] In genotype 2 and 3 patients, SVR rates with sofosbuvir were based on POSITRON (INF-ineligible) and FUSION (treatment-experienced), while SVR rates for Peg-INF/RBV (treatment-experienced only) were based on historical controls, and SVR rate for no treatment were based on POSITRON (INF-ineligible) or assumed to be 0% (treatment-experienced).

The cumulative incidence of complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) over a patient's lifetime was forecasted using transition probabilities based on different sources. The manufacturer assumed that patients achieving SVR were essentially cured and did not progress to develop complications. Difference in risk of adverse events (anemia, depression, rash) was obtained from different studies. Health state utility values were derived from Hsu et al.[3] During the natural disease progression phase, utility changes were dependent on whether the patient has achieved SVR or if disease is progressing. Treatment-related utility decrements were applied to reflect the decrease in patients' quality of life while on antiviral therapy.[3] SVR-related utility increment was applied, based on John-Baptiste et al.[4] Drug costs were obtained from the Quebec Drug Formulary or from the manufacturer (for sofosbuvir). Duration of therapy, which had an impact on drug costs, was determined for each patient subgroup using clinical trial data. Initial input for the resource utilization pattern related to monitoring of patients was based on UK standards, but was reviewed by a Canadian hepatologist and was costed generally using standard Ontario sources. The costs to manage adverse events were obtained from a retrospective study of the Quebec provincial drug reimbursement program (Régie de l'assurance maladie du Québec). Liver disease health state costs were derived from Dakin et al.[5] and different assumptions.

Results of Manufacturer's Analysis

- In genotype 1 treatment-naive patients, sofosbuvir is a cost-effective treatment compared with Peg-INF/RBV (ICUR $31,323 per QALY and $1,197 per QALY in non-cirrhotic and cirrhotic patients, respectively), boceprevir, and telaprevir (ICURs below $20,000 per QALY for non-cirrhotic patients, and dominant in cirrhotic patients).
- In genotype 2 and 3 patients ineligible or unwilling to receive, or intolerant to interferon, ICUR for sofosbuvir compared with no treatment was below $20,000 per QALY for genotype 2, and below $60,000 per QALY for genotype 3.
- In genotype 2 patients who experienced a relapse or breakthrough to previous treatment with Peg-INF/RBV, sofosbuvir is cost-effective compared with no treatment (ICURs below $45,000 per QALY) and Peg-INF/RBV (ICURs below $17,000 per QALY). In genotype 2 patients non-responder to Peg-INF/RBV, compared with no treatment or Peg-INF/RBV, sofosbuvir had an ICUR below $22,000 per QALY in non-cirrhotic patients, but was dominated in cirrhotic patients.
- In genotype 3 patients who experienced a relapse or breakthrough to previous treatment with Peg-INF/RBV, sofosbuvir is cost-effective compared with no treatment (ICURs below $45,000 per QALY). Compared with Peg-INF/RBV, ICUR for sofosbuvir was $51,519 per QALY in non-cirrhotic patients, and $5,777 per QALY in cirrhotic patients. In genotype 3 patients non-responders to Peg-INF/RBV, the ICUR of sofosbuvir compared with no treatment or Peg-INF/RBV was $50,346, and $62,393, respectively in non-cirrhotic patients. In cirrhotic patients, the ICUR for sofosbuvir versus no treatment or Peg-INF/RBV was below $24,000 per QALY.

Interpretations and Key Limitations

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

- The design of NEUTRINO and FUSION required use of historical controls and naive indirect comparisons, which generates uncertainty in the ICURs.
- Many of the comparisons were based on very small sample size and results in some subgroups were not consistent with overall findings from FUSION and POSITRON; e.g., cirrhotic patients presenting better SVR rates than non-cirrhotic patients.
- Potential longer duration of therapy with sofosbuvir in genotype 3 patients was not considered.

Common Drug Review Analyses

CDR noted uncertainty in a number of key parameters of the model. The following parameters were considered in reanalyses: Saskatchewan Drug Benefit costs; more conservative SVR estimates for sofosbuvir, based on the lower bounds of the 95% confidence interval or credible intervals limits; utility increment assigned to patients who achieved SVR was reduced from 0.08[4] to 0.07;[3,6] time horizon was shortened to 80 years of age instead of 100; a lower cost of anemia was used.[7]

- In genotype 1 treatment-naive non-cirrhotic patients, the cost-effectiveness of sofosbuvir compared with telaprevir, boceprevir, and Peg-INF/RBV is uncertain, due to lack of a direct comparator in the NEUTRINO trial, and wide credible intervals in the manufacturer's NMA. Using SVR estimates from the NMA, the ICUR for sofosbuvir versus Peg-INF/RBV, telaprevir, and boceprevir was $50,266 per QALY, $11,531 per QALY, and $14,030 per QALY, respectively. Using conservative SVR estimates, the ICUR for sofosbuvir versus Peg-INF/RBV was $135,391 per QALY, and sofosbuvir was dominated by telaprevir and boceprevir. In cirrhotic patients, using a conservative estimate, sofosbuvir had an ICUR of $7,119 per QALY versus Peg-INF/RBV and $3,237 per QALY versus boceprevir, but was dominated by telaprevir.
- In genotype 2 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir versus no treatment remained attractive, in both non-cirrhotic and cirrhotic patients ($28,983 and $3,268 per QALY, respectively). In genotype 2 patients with prior-relapse or breakthrough, sofosbuvir was generally cost-effective versus no treatment and versus Peg-INF/RBV (ICURs ranging from $23,944 to $31,487 per QALY), except versus Peg-INF/RBV in cirrhotic patients ($62,162 per QALY). In genotype 2 prior non-responders, the ICUR for sofosbuvir compared with no treatment or Peg-INF/RBV were less attractive in in non-cirrhotic patients (ranging from $61,564 to $136,936), and sofosbuvir was dominated by Peg-INF/RBV and no treatment in cirrhotic patients.
- In genotype 3 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir versus no treatment were above $75,000 per QALY, in both non-cirrhotic and cirrhotic patients. In genotype 3 patients with prior-relapse or breakthrough, sofosbuvir was not cost-effective (either dominated or ICURs > $150,000 per QALY) versus no treatment and versus Peg-INF/RBV in non-cirrhotic patients, but ICURs were below $31,000 per QALY in cirrhotic patients. In prior non-responders, compared with no treatment and Peg-INF/RBV, sofosbuvir was either dominated, or had ICURs above $150,000 per QALY.

Conclusions

The ICURs of sofosbuvir versus appropriate comparators varied widely across genotypes and various subgroups. Analyses in genotype 1 patients were limited by lack of direct comparative data. Most of the analyses in genotype 2 and genotype 3 patients were limited by the small sample size of the clinical trials used to inform efficacy inputs. Based on CDR reanalyses, sofosbuvir is likely cost-effective in the following subgroups: genotype 1 treatment-naive cirrhotic patients (compared with boceprevir and Peg-INF/RBV, but analyses were based on very small subgroups, and on a naive indirect treatment comparison); genotype 2 Peg-INF/RBV-ineligible and prior-relapsers or breakthrough (except cirrhotic patients) compared with no treatment and Peg-INF/RBV; genotype 3 prior-relapsers or breakthrough with cirrhosis, compared with no treatment and Peg-INF/RBV.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

What is the incremental cost-effectiveness of sofosbuvir in treatment of chronic hepatitis C (CHC) infection versus appropriate comparators, over a lifetime horizon and from a publicly funded health care system perspective, in patients with all genotypes of chronic hepatitis C virus (HCV) infection?

1.2 Treatment

- Genotype 1 treatment-naive: sofosbuvir 400 mg daily in combination with pegylated interferon plus ribavirin (Peg-INF/RBV) for 12 weeks
- Genotype 2: sofosbuvir 400 mg daily in combination ribavirin (RBV) for 12 weeks
- Genotype 3: sofosbuvir 400 mg daily in combination RBV for 16 weeks.

1.3 Comparators

- Genotype 1 treatment-naive: Peg-INF/RBV for 48 weeks, telaprevir for 12 weeks plus Peg-INF/RBV for 24 to 48 weeks, boceprevir for 24 to 44 weeks plus Peg-INF/RBV for 28 to 48 weeks
- Genotype 2: No treatment, Peg-INF/RBV for 48 weeks (treatment-experienced)
- Genotype 3: No treatment, Peg-INF/RBV for 48 weeks (treatment-experienced).

The manufacturer noted that for treatment-experienced patients with genotype 2 or 3, no treatment should be considered to be the most appropriate comparator. However, Canadian 2012 guidelines on the management of CHC indicate that in patients with genotype 2 or 3 who have failed a previous 24-week course of Peg-INF/RBV and have at least stage 2 fibrosis, retreatment with a 48-week course of Peg-INF/RBV may be considered.[8] Results from the manufacturer's base-case analysis comparing sofosbuvir+Peg-INF/RBV with Peg-INF/RBV for 48 weeks in these patients will therefore also be reported.

Simeprevir in combination with Peg-INF/RBV was not included as a comparator for treatment-naive genotype 1 patients. However, it was not listed by any of the public drug plans at the time of the review.

1.4 Type of Economic Evaluation

A cost-utility analysis (CUA) was undertaken and is appropriate according to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines. The perspective was that of a ministry of health.

1.5 Population

The target population (pertaining to the reimbursement ask) for the economic analysis consisted of CHC genotype 1 treatment-naive patients, genotype 2 and 3 treatment-naive patients who where interferon (INF)-ineligible or treatment-experienced patients (INF-intolerant, non-responders, and prior relapse or breakthrough) who were considered suitable candidates for sofosbuvir therapy. Patients entering the model were either cirrhotic or not. They had a mean age at baseline of 45 years and 56.3% were males.

a) INF-Ineligible Patients

Patients presenting comorbidities deemed at risk for worsening with interferon treatment, including autoimmune disorders, significant psychiatric disorder, seizure disorder, poorly controlled thyroid

dysfunction, retinal disease, poorly controlled diabetes, or other relative interferon contraindication that may have been approved after discussion with the medical monitor (based on the POSITRON trial). Most of the patients were considered ineligible due to psychiatric disease (57%) and autoimmune disease (19%).

b) INF-Unwilling

Medical records documenting the patient's decision to decline treatment with an INF-based regimen at three months or more prior to signing the informed consent (based on the POSITRON trial).

c) INF-Intolerant

Patients who completed 12 or fewer weeks of treatment (ending three months or more prior to screening) with INF and discontinued treatment due to development or significant worsening of at least one of the following conditions: significant local or systemic adverse reaction to INF, psychiatric disease, significant cognitive impairment, neuropathy, disabling flu-like syndrome, gastrointestinal toxicity, thrombocytopenia, neutropenia, or autoimmune disorders (based on the POSITRON trial).

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

2. METHODS

Please see Table 19 for the key limitations associated with the methodology used by the manufacturer.

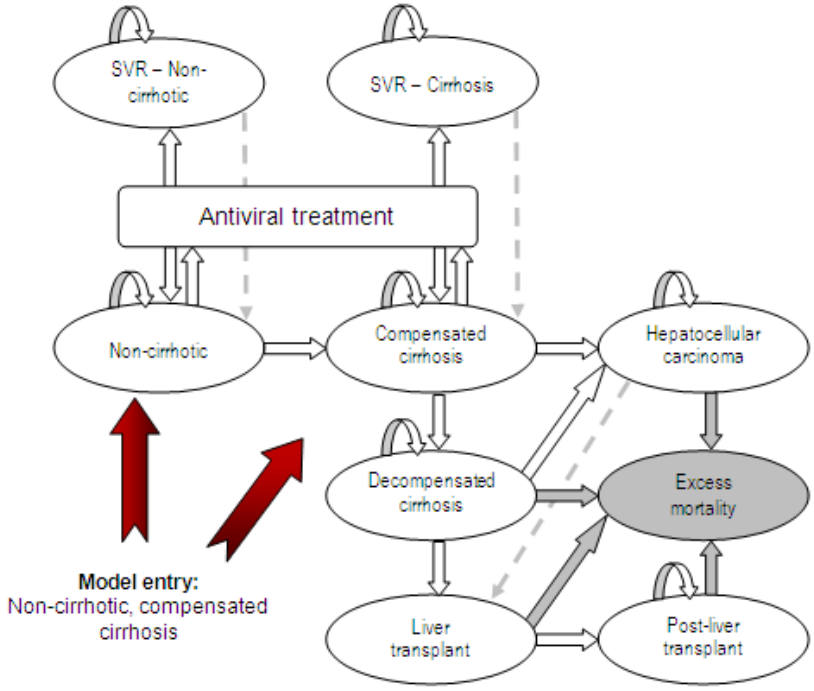
2.1 Model Structure

At baseline, patients enter the model according to their cirrhotic status.

Patients receive the assigned treatment regimen from the different clinical trials' protocols and may or may not experience adverse events. At the end of therapy:

- patients with detectable HCV-RNA are considered treatment failures and will remain in their original CHC health state
- patients with undetectable HCV-RNA at 12 or 24 weeks are considered to have a sustained virologic response (SVR), or be cured from viral infection
- if patients have detectable HCV-RNA at the 24-week follow-up point, they are considered to have had a relapse and remain in their original chronic HCV health state.

FIGURE 1: SCHEMATIC OF CHRONIC HEPATITIS C MARKOV MODEL



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

SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[9]

The long-term clinical outcomes are extrapolated with the Markov model incorporating the natural disease progression of CHC. All-cause mortality was applied to all health states. The cycle length was one year.

Patients without an SVR faced an annual probability of progressing from no cirrhosis to compensated cirrhosis as if they had not received antiviral treatment.

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 or hepatocellular carcinoma.

Without a successful treatment, patients may remain in their current health state or progress to more severe stages of liver disease, liver transplant, and death.

2.2 Clinical Inputs

a) Efficacy

In general, SVR rates were obtained from pivotal clinical trials. Without head-to-head trials comparing the efficacy and safety of direct-acting antiviral agent (DAA) plus Peg-INF/RBV regimens for the genotype 1 treatment-naive population, clinical inputs of the pivotal trials for each of the comparators were regrouped in the comparative model and results were stratified for the cirrhotic and non-cirrhotic populations. SVR results of the NEUTRINO (Lawitz[10]), IDEAL (McHutchison[11]), ADVANCE (Jacobson[12]), and SPRINT-2 (Poordad[13]) served as primary data sources for sofosbuvir, INF, telaprevir, and boceprevir, respectively.

For genotype 2 and 3 populations ineligible or unwilling to receive, or intolerant to Peg-INF, the POSITRON trial[14] results were considered. The manufacturer considered that the appropriate comparator was no treatment. For the genotype 2 and 3 treatment-experienced populations, the FUSION trial[14] results served to input the model for patients who were non-responders, or who had had a relapse or breakthrough on previous Peg-INF therapy. The manufacturer considered that the appropriate comparator was no treatment.

TABLE 2: SVR RATES USED IN THE MANUFACTURER'S MODEL FOR SOF AND COMPARATORS BY SUBGROUPS

Subgroup	SVR Rates (%), 95% CI[a]				
	SOF	Peg-INF-2a	BOC	TEL	No Treatment
G1 TN — non-cirrhotic patients	91.3 (86.9 to 94.5)	43.6 (40.3 to 46.9)	69.5 (64.0 to 74.8)	77.9 (73 to 82.5)	NA
G1 TN — cirrhotic patients	80.8 (67.5 to 90.4)	23.6 (16.2 to 32)	50.0 (31.3 to 68.7)	61.6 (50.3 to 72.4)	NA
G2 TN — INF-ineligible non-cirrhotic patients	91.8 (85.1 to 96.6)	NA	NA	NA	0%
G2 TN — INF-ineligible cirrhotic patients	93.3 (76.8 to 99.8)	NA	NA	NA	0%
G2 TE — INF-intolerant non-cirrhotic patients	100 (59 to 100)	NA	NA	NA	0%
G2 TE — INF-intolerant cirrhotic patients	100 (15.8 to 100)	NA	NA	NA	0%

Subgroup	SVR Rates (%), 95% CI[a]				
	SOF	Peg-INF-2a	BOC	TEL	No Treatment
G2 TE — INF-non-responder, non-cirrhotic patients	87.5 (47.3 to 99.7)	25 (17.1 to 33.9)	NA	NA	0%
G2 TE — INF-non-responder, cirrhotic patients	0%	18.9 (15.1 to 22.7)	NA	NA	0%
G2 TE — relapse or breakthrough non-cirrhotic patients	100 (81.5 to 100)	25 (17.1 to 33.9)	NA	NA	0%
G2 TE — relapse or breakthrough cirrhotic patients	75 (34.9 to 96.8)	18.9 (15.1 to 22.7)	NA	NA	0%
G3 TN — INF-ineligible non-cirrhotic patients	66.7 (41 to 86.7)	NA	NA	NA	0%
G3 TN — INF-ineligible cirrhotic patients	22.2 (25.3 to 43.7)	NA	NA	NA	0%
G3 TE — INF-intolerant non-cirrhotic patients	100 (81.5 to 100)	NA	NA	NA	0%
G3 TE — INF-intolerant cirrhotic patients	20 (25.3 to 43.7)	NA	NA	NA	0%
G3 TE — INF-non-responder, non-cirrhotic patients	58.3 (27.7 to 84.8)	25 (17.1 to 33.9)	NA	NA	0%
G3 TE — INF-non-responder, cirrhotic patients	40 (5.3 to 85.3)	10.4 (8.3 to 12.5)	NA	NA	0%
G3 TE — relapse or breakthrough non-cirrhotic patients	64.3 (27.7 to 84.8)	25 (17.1 to 33.9)	NA	NA	0%
G3 TE — relapse or breakthrough cirrhotic patients	66.7 (41 to 86.7)	10.4 (8.3 to 12.5)	NA	NA	0%

BOC = boceprevir; G = genotype; INF = interferon; NA = not applicable; Peg-INF-2a = pegylated interferon alpha-2a; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive.
[a]Confidence intervals of 95% were not presented in the manufacturer's report and were taken directly from the Excel model (deterministic sensitivity analysis inputs sheet).
Source: Manufacturer's pharmacoeconomic submission.[9]

An alternate analysis was carried out using a manufacturer-funded unpublished network meta-analysis (NMA).[2] A summary and critical appraisal of the NMA submitted by the manufacturer is presented in Appendix 7 of the Common Drug Review (CDR) Clinical Review.

Results from the NMA that were used to inform the economic model are presented in Table 3. When considering a 95% credible interval (CrI), the primary analysis of the NMA showed no significant difference between sofosbuvir and boceprevir and between sofosbuvir and telaprevir with regard to the SVR rates (even if point estimates tend to be in favour of sofosbuvir).

TABLE 3: NMA RESULTS USED IN THE ALTERNATE ANALYSIS OF THE PHARMACOECONOMIC MODEL: ODDS RATIO OF ACHIEVING SVR

Comparison	Primary Analysis (OR and 95% CrI)
SOF-12 vs. Peg-INF-2a	8.67 (1.88 to 45.4)
BOC-SDT vs. Peg-INF-2a	2.69 (1.07 to 5.99)
BOC-RGT vs. Peg-INF-2a	2.22 (0.73 to 5.62)
TEL-SDT vs. Peg-INF-2a	3.32 (1.12 to 9.83)
TEL-RGT vs. Peg-INF-2a	3.77 (1.46 to 9.44)
SOF-12 vs. BOC-SDT	3.29 (0.58 to 21.5)
SOF-12 vs. BOC-RGT	3.97 (0.67 to 29.0)
SOF-12 vs. TEL-SDT	2.61 (0.40 to 18.7)
SOF-12 vs. TEL-RGT	2.28 (0.39 to 15.2)

BOC = boceprevir; CrI = credible interval; NMA = network meta-analysis; OR = odds ratio; Peg-INF-2a = pegylated interferon alpha-2a; RGT = response-guided therapy; SDT = standard-duration therapy; SOF-12 = sofosbuvir (12-week treatment duration); SOF-24 = sofosbuvir (24-week treatment duration); SVR = sustained virologic response; TEL = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

b) Treatment Duration

Treatment durations vary by genotype, by drug, by regimen, and by futility rules. Treatments can be discontinued due to adverse events or personal choice. Data from clinical trials were used to determine weighted actual treatments duration by subgroup.

An important limitation of the model is that it does not consider duration of treatment exceeding 16 weeks in patients with genotype 3, which is not consistent with the product monograph, the VALENCE trial,[15] and recent guidelines, such as the European Association for the Study of the Liver (EASL) guidelines,[16] which recommend that if used with ribavirin only, a 24-week course of sofosbuvir should be used in genotype 3 patients (12 weeks if used in combination with Peg-INF/RBV).

TABLE 4: MEAN TREATMENT DURATIONS APPLIED IN THE MODEL BY TREATMENT POPULATIONS

Population	Comparator	Mean Duration (Weeks)
G1 TN	SOF + Peg-INF/RBV	11.8
	TEL + Peg-INF/RBV	
	TEL	11.9
	Peg-INF/RBV	26.9
	BOC + Peg-INF/RBV	
	BOC	27.1
	Peg-INF/RBV	31.1
	Peg-INF/RBV	38.4
G2 TN, INF-ineligible, unwilling	SOF + RBV	11.8
G2 TE, INF-intolerant	SOF + RBV	12.0
G2 TE, non-responders	SOF + RBV	12.0
	Peg-INF/RBV	44.8
G2 TE, relapse or breakthrough	SOF + RBV	12.0
	Peg-INF/RBV	44.8
G3 TN, INF-ineligible, unwilling	SOF + RBV	15.7
G3 TE, INF-intolerant	SOF + RBV	15.4

Population	Comparator	Mean Duration (Weeks)
G3 TE, non-responders	SOF + RBV	16.0
	Peg-INF/RBV	44.2
G3 TE, relapse or breakthrough	SOF + RBV	16.0
	Peg-INF/RBV	45.8

BOC = boceprevir; G = genotype; INF = interferon; Peg-INF/RBV = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; TEL = telaprevir; TE = treatment-experienced; TN = treatment-naive.
Source: Manufacturer's pharmacoeconomic submission.[9]

c) Harms

Adverse events included in the model were those that the manufacturer deemed to be the most common and that require medical interventions: anemia, depression, and rash. A Régie de l'assurance maladie du Québec (RAMQ) database unpublished study identified a high frequency and costs for these events. In the model, irrespective of grade, adverse events were considered based on overall frequency observed in the pooled clinical trials (for sofosbuvir) and from product monographs (for boceprevir and telaprevir). For Peg-IFN/RBV, frequencies were retrieved from product monographs, except for anemia, for which the data sources were the IDEAL[11] and FISSION[10] studies.

TABLE 5: ADVERSE EVENTS RATES USED IN THE HEALTH ECONOMIC MODEL

Regimen	Population	Anemia	Rash	Depression
BOC + Peg-INF/RBV	G1 TN	50.0%	18.0%	23.0%
TEL + Peg-INF/RBV	G1 TN	31.8%	48.7%	0.0%
Peg-INF-2a or 2b + RBV	G1 G2 and G3	34.0% 11.5%	5.0% 9.0%	28.0% 21.0%
SOF + Peg-INF/RBV	G1 G2 and G3	20.8% 9.3%	18.0% 9.0%	9.5% 6.0%

BOC = boceprevir; G = genotype; Peg-INF-2a = pegylated interferon alpha-2a; Peg-INF-2b = pegylated interferon alpha-2b; Peg-INF/RBV = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; TPV = telaprevir.
Source: Manufacturer's pharmacoeconomic submission.[9]

d) Disease Progression or Transition Probabilities

The most recent health technology assessments (HTAs) were selected to populate the model transition probabilities shown in Table 6.

TABLE 6: TRANSITION PROBABILITIES USED IN THE ECONOMIC MODEL

From	To	Value	Source
Non-cirrhotic	CC (30 years) — non-G1	0.090	Grischenko et al. 2009,[17] Thomson et al. 2008[18]
	CC (30 years) — G1	0.006	
	CC (40 years) — non-G1	0.014	
	CC (40 years) — G1	0.010	
	CC (50 years) — non-G1	0.025	
	CC (50 years) — G1	0.016	
CC	DCC	0.04	Fattovich et al. 1997[19]
	HCC	0.01	
DCC	HCC	0.01	Fattovich et al. 1997[19]
	LT	0.03	Shepherd et al. 2007[20]
	death	0.13	Fattovich et al. 1997[19]
HCC	Liver-related death	0.43	Fattovich et al. 1997[19]
LT	Liver-related death (year 1)	0.21	Shepherd et al. 2007[20]
	Liver-related death (year 2+)	0.06	

CC = compensated cirrhosis; DCC = decompensated cirrhosis; G = genotype; HCC = hepatocellular carcinoma; LT = liver transplant.
Source: Manufacturer's pharmacoeconomic submission.[9]

e) Mortality

All-cause mortality was obtained from age- and sex-specific Life Tables for Canada 2007-2009 (Statistics Canada), assuming a 50:50 split by gender.

f) Costs

Resource use was considered from the perspective of the Ministry of Health. Costs considered were drug costs, monitoring costs, adverse event costs, and health state costs.

Drug Costs

The cost of sofosbuvir was obtained from the manufacturer [redacted] per day).

The cost of comparators was based on the Quebec Drug Formulary (excluding mark-up and wholesaler).

Monitoring Costs

Frequency, type, and quantity of resources were retrieved from a previous UK HTA assessment and modified by a Canadian hepatologist. The resource utilization pattern was then costed using standard Ontario and Alberta sources, but also using surveys and personal communications.

Adverse Event Costs

Costs related to the management of anemia, rash, and depression were based on an unpublished retrospective study of the Quebec RAMQ database.[9,21,22]

TABLE 7: COST OF ADVERSE EVENTS

Adverse Event	Specialist Costs	Medication Costs	Cost of Event (C$)
Anemia	$9	$10,795	$10,666
Depression	$5	$261	$268
Rash	$13	$64	$78

Source: Manufacturer's pharmacoeconomic submission.[9]

Health State Costs

The majority of health state costs were obtained from the Dakin et al. study.[5] For patients achieving SVR, it was assumed that non-cirrhotic patients would require no other hepatic specific care and that cirrhotic patients would require one hepatologist consultation, ultrasounds, laboratory measures, liver function tests, and blood counts.

g) Utilities

Health state utilities were obtained from the study by Hsu et al.[3] This study was selected because it was the most recent Canadian study and had the largest sample size of studies considered.[3,4,6,23] Health utility index (HUI) 2 and time trade-off (TTO) results were available, but the HUI 2 utilities were used in the model because they better differentiated between health states.

Treatment-related utility decrements were applied to reflect the decrease in health-related quality of life that patients experience while on antiviral therapy. The model assumes that these utility decrements apply during treatment. Utility decrements were derived from Hsu 2012.[3]

A utility increment was considered for patients achieving SVR based on a Canadian study investigating quality of life in post-SVR patients.[4]

TABLE 8: HEALTH STATE UTILITIES IN THE MANUFACTURER'S BASE-CASE ANALYSIS DERIVED FROM STUDY BY HSU (2012) (AND FROM JOHN-BAPTISTE [2009] FOR SVR UTILITY INCREMENT)

Health States	Utility Values — TTO	Utility Values — HUI 2
CHC treatment SVR	0.81 0.88	0.71 0.80
Mild or moderate CHC	0.80	0.73
Compensated cirrhosis	0.78	0.69
Decompensated cirrhosis		
Hepatocellular carcinoma	0.78	0.72
Post-transplant	0.89	0.75
Treatment utility decrement		−0.0274
SVR utility increment	0.08[a]	

CHC = chronic hepatitis C; HUI = health utility index; SVR = sustained virologic response; TTO = time trade-off.
[a]From John-Baptiste study (2009).[4]
Source: Manufacturer's pharmacoeconomic submission.[9]

h) Time Horizon

The model used a lifetime horizon (100 years of age) that allowed the capture of all the essential consequences of the disease. The time horizon could be varied in the model from 50, 60, 80, to 100 years. Mean age of the patients entering the model was 49 years, in concordance with sofosbuvir clinical trial data. Cycle length was three months for the first two years and one year thereafter.

This time horizon is consistent with other economic models of Hepatitis C that were developed by HTA agencies.[24,25]

i) 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.

j) Validation

The model validation process is not described in the manufacturer's pharmacoeconomic submission.

3. RESULTS

3.1 Manufacturer's Base Case

a) Overall Sustained Virologic Response Rates and Cumulative Incidences of Severe Liver Disease

The model simulation allowed for the estimation over the lifetime horizon of the probability of SVR, the number of cirrhosis cases (per 10,000), the number of hepatocellular carcinoma (HCC) cases (per 10,000), and the number of liver transplants (per 10,000). Results of the simulation are shown in Appendix 3: Summary Table OF Common Drug Review Reanalyses.

b) Incremental Cost per Quality-Adjusted Life-Year

Base-case results are presented in Table 9.

TABLE 9: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Incremental Total Costs ($)	Incremental SVR Rate (%)	Incremental QALYs	Incremental Cost per Life-Year Gained	Incremental Cost per QALY Gained
G1 TN — non-cirrhotic patients					
SOF vs. Peg-INF/RBV	$26,950	47%	0.86	$133,413	$31,323
SOF vs. TEL	$1,335	13.4%	0.26	$23,199	$5,076
SOF vs. BOC	$6,374	21.8%	0.41	$63,491	$15,599
G1 TN — cirrhotic patients					
SOF vs. Peg-INF/RBV	$2,745	57%	2.64	$1,020	$1,039
SOF vs. TEL	−$7,671	19.2%	0.92	SOF dominates	SOF dominates
SOF vs. BOC	−$7,791	30.8%	1.48	SOF dominates	SOF dominates
G2 TN — INF-ineligible non-cirrhotic patients					
SOF vs. no treatment	$34,366	91.8%	1.75	$55,160	$19,614
G2 TN — INF-ineligible cirrhotic patients					
SOF vs. no treatment	$180	93.3%	4.45	$38	$40
G2 TE — INF-intolerant non-cirrhotic patients					
SOF vs. no treatment	$33,959	100%	1.91	$49,858	$17,765
G2 TE — INF-intolerant cirrhotic patients					
SOF vs. no treatment	−$2,445	100%	4.77	SOF dominates	SOF dominates
G2 TE — INF non-responder, non-cirrhotic patients					
SOF vs. no treatment	$35,912	87.5%	1.67	$60,566	$21,509
SOF vs. Peg-INF/RBV	$19,668	63%	1.20	$51,751	$16,446
G2 TE — INF non-responder, cirrhotic patients					
SOF vs. no treatment	$50,056	0%	–0.07	SOF is dominated	SOF is dominated
SOF vs. Peg-INF/RBV	$38,885	–19%	–1.05	SOF is dominated	SOF is dominated
G2 TE — relapse or breakthrough non-cirrhotic patients					
SOF vs. no treatment	$33,959	100%	1.91	$49,858	$17,765
SOF vs. Peg-INF/RBV	$17,719	75%	1.44	$37,842	$12,323
G2 TE — relapse or breakthrough cirrhotic patients					
SOF vs. no treatment	$10,680	75%	3.56	$2,858	$2,999
SOF vs. Peg-INF/RBV	–$487	56%	2.58	Sofosbuvir	Sofosbuvir

	Incremental Total Costs ($)	Incremental SVR Rate (%)	Incremental QALYs	Incremental Cost per Life-Year Gained	Incremental Cost per QALY Gained
				dominates	dominates
G3 TN — INF-ineligible non-cirrhotic patients					
SOF vs. no treatment	$53,106	66.7%	1.27	$119,077	$41,935
G3 TN — INF-ineligible cirrhotic patients					
SOF vs. no treatment	$52,332	22.2%	1.00	$50,437	$52,125
G3 TE — INF-intolerant non-cirrhotic patients					
SOF vs. no treatment	$46,902	100%	1.91	$68,860	$24,536
G3 TE — INF-intolerant cirrhotic patients					
SOF vs. no treatment	$52,498	20%	0.90	$56,821	$58,571
G3 TE — INF non-responder, non-cirrhotic patients					
SOF vs. no treatment	$55,637	58.3%	1.11	$143,695	$50,346
SOF vs. Peg-INF/RBV	$39,393	33%	0.63	$226,029	$62,393
G3 TE — INF non-responder, cirrhotic patients					
SOF vs. no treatment	$44,223	40%	1.87	$22,716	$23,709
SOF vs. Peg-INF/RBV	$28,811	30%	1.27	$23,109	$22,652
G3 TE — relapse or breakthrough non-cirrhotic patients					
SOF vs. no treatment	$54,707	64.3%	1.22	$127,469	$44,831
SOF vs. Peg-INF/RBV	$38,463	39%	0.75	$177,832	$51,519
G3 TE — relapse or breakthrough cirrhotic patients					
SOF vs. no treatment	$30,223	66.7%	3.16	$9,129	$9,573
SOF vs. Peg-INF/RBV	$14,811	57%	2.56	$5,673	$5,777

BOC = boceprevir; G = genotype; INF = interferon; Peg-INF-2a = pegylated interferon alpha-2a; Peg-INF-2b = pegylated interferon alpha-2b; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir; TE = treatment-experienced; TN = treatment-naive.
Source: Manufacturer's pharmacoeconomic submission.

3.2 Summary of the Manufacturer's Sensitivity Analyses

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

Moreover, for genotype 1 treatment-naive non-cirrhotic patients, results of an alternate analysis based on an unpublished NMA were presented.[2]

TABLE 10: SUMMARY OF RESULTS OF THE MANUFACTURER'S ALTERNATE ANALYSIS BASED ON NMA FOR G1 TN NON-CIRRHOTIC PATIENTS

	Incremental Total Costs ($)	Incremental SVR Rate (%)	Incremental QALYs	Incremental Cost per Life-Year Gained	Incremental Cost per QALY Gained
SOF vs. Peg-INF/RBV	$27,981	39%	0.72	174,415	$38,992
SOF vs. TEL	$1,702	11%	0.21	$39,962	$8,027
SOF vs. BOC	$6,546	20%	0.38	$70,082	$17,014

BOC = boceprevir; G = genotype; NMA = network meta-analysis; QALY = quality-adjusted life-year; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir; TN = treatment-naive.

The incremental cost-utility ratios (ICURs) estimated in the alternate analysis are higher than those in the base case.

a) Deterministic Sensitivity Analyses

For each subgroup, model parameters were varied separately. The sofosbuvir SVR rate was varied within the limits of the 95% confidence intervals (CI) from clinical trials. Comparator SVR rates were varied within the limits of the 95% CI, or by varying by ± 20% the base-case value. Incidence of adverse events, health states costs, transition probabilities, and background mortality rate were varied over a ± 25% range. Utility values were varied over a ± 20% range and discount rate was varied using values of 0% and 3%.

b) Probabilistic Sensitivity Analysis

Simulations were processed to represent the uncertainty of model results by varying some parameters (utility values, health states costs, transitional probabilities, and SVR [and odds ratios for the alternate analysis]) by random draws from their assumed distributions. Based on the simulations, a scatterplot and an acceptability curve were drawn to estimate the probability of sofosbuvir being considered cost-effective against its comparator treatments at a given willingness-to-pay threshold per quality-adjusted life-year (QALY) gained.

The design of the model did not allow a probabilistic sensitivity analysis, which would allow for a comparison of all treatment options simultaneously. This approach would have been preferable.

Deterministic and probabilistic sensitivity analysis results for each selected population are shown in Table 22, Appendix 2: Additional Results From Manufacturer's Base-Case And Sensitivity Analyses.

For the majority of subgroups, deterministic sensitivity analyses had only a modest impact on results. Parameters with the largest impact on results (apart from discounting) were utility value of the cirrhotic health state, SVR rate of comparator, and cost of health states (cirrhotic disease).

3.3 Common Drug Review Analyses

CDR reviewers performed several additional sensitivity analyses in each of the selected populations.

The following parameters were changed for all reanalyses (CDR Analysis A):

- Saskatchewan Drug Benefit costs instead of Quebec RAMQ costs were applied. Note that the only difference was for the cost of boceprevir.
- Given uncertainty in comparative SVR rates due to indirect comparisons, and very small sample sizes for some subgroups, more conservative SVR estimates were used, based on the 95% CI (or CrI) limits or assumptions (± 15%) if no CI was available.
- The manufacturer applied a 0.08 utility increment for patients achieving SVR, based on John-Baptiste et al.[4] Lower utility increments have been reported in the literature, such as 0.04 and 0.07.[6] CDR selected a more conservative utility increment of 0.07 for the reanalyses, which was consistent with Chong et al. and Hsu l.[3,6]
- The time horizon was shortened to 80 years of age instead of 100.
- A lower cost of anemia was used. The manufacturer estimated that 25% of patients would receive erythropoietin, yielding a cost of $2,666.50. Based on Gao et al.,[7] in which a 22% utilization of erythropoietin was reported, as well as clinical experts' input estimating that approximately 10% of

patients will require erythropoietin, the RAMQ total cost of anemia was multiplied by 16%, yielding a cost of $1,706.60.

a) Results

A summary table of all CDR reanalyses is presented in Appendix 3: Summary Table OF Common Drug Review Reanalyses.

Genotype 1 Treatment-Naive Non-cirrhotic Patients

The manufacturer's base-case efficacy inputs were based on a naive indirect comparison, and did not account for potential variations in Peg-INF/RBV response across trials. The manufacturer's alternate analysis using the NMA results was considered to be a more appropriate analysis, although limitations were noted, as discussed in Appendix 7 of the CDR clinical review report. Given the lack of good direct comparative data and the CDR appraisal of the NMA, and considering the wide 95% CrI around the NMA ORs results (primary analysis), sofosbuvir comparative cost-effectiveness remains uncertain.

Based on the NMA, there was no statistically significant difference between sofosbuvir, telaprevir, and boceprevir when considering the 95% CrI around SVR OR. Consequently, as presented in Table 11, using more conservative assumptions based on the SVR OR's 95% CrI results, sofosbuvir was dominated by telaprevir and boceprevir, and presented an ICUR of $135,391 versus Peg-INF/RBV.

TABLE 11: CDR REANALYSIS (G1 TN NON-CIRRHOTIC PATIENTS): ICURS FOR SOFOSBUVIR VERSUS EACH COMPARATOR

	Base-case analysis submitted by manufacturer ICUR SOF vs. comparator	CDR Analysis A Reanalysis by CDR using NMA results, SK costs, utility increment (0.07), 80-years time horizon, and lower cost of anemia ICUR SOF vs. comparator	CDR Analysis B CDR Analysis A + lower bound of NMA CrI OR SVR sofosbuvir vs. Peg-INF/RBV 1.88 ICUR SOF vs. comparator
SOF vs. Peg-INF/RBV	$31,323	$50,266	$135,391
SOF vs. TEL	$5,076	$11,531	Dominated
SOF vs. BOC	$15,599	$14,030	Dominated

BOC = boceprevir; CDR = Common Drug Review; CrI = credible interval; G = genotype; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; OR = odds ratio; Peg-INF/RBV = pegylated interferon plus ribavirin; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir; TN = treatment-naive.

Genotype 1 Treatment-Naive Cirrhotic Patients

Only 17% of the NEUTRINO population was cirrhotic. In addition to the lack of direct comparative data (efficacy and quality of life), this increases pharmacoeconomic uncertainty. As ICURs are estimated based on individual drugs' study results (naive indirect comparison), this subgroup analysis could be more prone to bias. As shown in Table 12, when considering the lower bound of the 95% CI for SVR rate from NEUTRINO (67.5%), ICURs for sofosbuvir versus comparators remain attractive. However, when assumptions are made for telaprevir and boceprevir SVR rates uncertainty (+15%), sofosbuvir is dominated by telaprevir but still remains pharmacoeconomically attractive when compared with boceprevir.

In addition, it must be considered that telaprevir and boceprevir were both recommended by the Canadian Drug Expert Committee conditional on a reduced price. Possible lower prices were not considered by the manufacturer and would have negatively affected sofosbuvir ICURs (which would have been higher). Based on these reasons, sofosbuvir cost-effectiveness results in this subgroup should be considered to be hypothesis-generating only.

TABLE 12: CDR REANALYSIS (G1 TN CIRRHOTIC PATIENTS): ICURS FOR SOFOSBUVIR VERSUS EACH COMPARATOR

	Base-Case Analysis Submitted by Manufacturer	Lower Bound of the 95% CI for SVR Rate SOF (66.5%)	+15% SVR Rate for TEL and BOC	Exploratory Analysis 15% Reduction in TEL and BOC Price
	ICUR SOF vs. Comparator	ICUR SOF vs. Comparator	ICUR SOF vs. Comparator	ICUR SOF vs. Comparator
SOF vs. Peg-INF/RBV	$1,039	$7,119	N/A	N/A
SOF vs. TEL	SOF dominates	SOF dominates	SOF is dominated	$26,483
SOF vs BOC	SOF dominates	SOF dominates	$3,237	$2,519

BOC = boceprevir; CI = confidence interval; ICUR = incremental cost-utility ratio; Peg-INF/RBV = pegylated interferon plus ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir.

Genotype 2 Treatment-Naive Interferon-Ineligible or Unwilling and Treatment-Experienced Interferon-Intolerant Non-cirrhotic and Cirrhotic Patients

In POSITRON, the number of genotype 2 patients in the sofosbuvir group who were intolerant to Peg-INF/RBV was small (n = 9). The SVR rate in these patients was 100% for both non-cirrhotic and cirrhotic patients, which is higher than that reported for ineligible or unwilling patients (91.8% and 93.3% for non-cirrhotic and cirrhotic patients, respectively). The POSITRON study did not conclude that ineligible or unwilling patients had a lower response than intolerant patients, and the CIs for SVR rates compared with placebo of the three groups overlapped. Furthermore, only a minority (7.7%) of intolerant patients in POSITRON had received 12 or more weeks of prior therapy, and thus the intolerant group was largely treatment naive.

For this reason, the analysis in interferon-intolerant patients presented by the manufacturer was considered to be too uncertain, and CDR considers that the analysis in genotype 2 treatment-naive ineligible or unwilling patients is a better representation of the cost-effectiveness of sofosbuvir compared with no treatment in patients in whom Peg-INF/RBV is not an option.

In addition to the changes presented earlier, to account for uncertainty in SVR rates, in a conservative scenario, the lower bound of the 95% confidence interval for sofosbuvir SVR rates was applied, based on values provided in the manufacturer's deterministic sensitivity analyses (Table 2). The results of the CDR reanalyses are presented Table 13. ICURs for sofosbuvir versus no treatment remained attractive in both non-cirrhotic and cirrhotic patients.

TABLE 13: CDR REANALYSIS (G2 TN INF-INELIGIBLE OR TE INF-INTOLERANT): ICURS FOR SOFOSBUVIR VERSUS NO TREATMENT

		Base-Case Analysis Submitted by Manufacturer	CDR Analysis A SK Costs, Utility Increment (0.07), 80-Years Time Horizon and Lower Cost of Anemia	CDR Analysis B Analysis A + Lower Bound of the 95% CI for SVR SOF
		ICUR SOF vs. No Treatment	ICUR SOF vs. No Treatment	ICUR SOF vs. No Treatment
Non-cirrhotic	INF-ineligible or unwilling	$19,614	$26,166	$28,983
	INF-intolerant	$17,765	N/A	N/A
Cirrhotic	INF-ineligible or unwilling	$40	$401	$3,268
	INF-intolerant	SOF dominates	N/A	N/A

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; INF=interferon; N/A = not applicable; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive.

Genotype 2 Treatment-Experienced Interferon Non-responders or Relapse or Breakthrough Non-cirrhotic and Cirrhotic Patients

The type of prior response to Peg-INF/RBV is an important predictor of response. Non-responders typically present lower SVR rates than patients with relapse or breakthrough. For this reason, even if the number of non-responders was small in FUSION (sofosbuvir group: n = 8 for non-cirrhotic, n = 2 for cirrhotic patients), both populations were considered separately in the CDR reanalyses.

In addition to changes presented earlier, to account for uncertainty in SVR rates, in a conservative scenario, the lower bound of the 95% CI for sofosbuvir SVR rates and upper bound of the 95% CI for Peg-INF/RBV SVR rates were applied, based on values provided in the manufacturer's deterministic sensitivity analyses (Table 2).

Results of the CDR reanalyses are presented in Table 14. In genotype 2 prior-relapse or breakthrough patients, sofosbuvir was generally cost-effective versus no treatment and versus Peg-INF/RBV (except for cirrhotic patients).

In genotype 2 prior non-responders, the ICUR for sofosbuvir compared with no treatment or Peg-INF/RBV was above commonly accepted thresholds in non-cirrhotic and was dominated in cirrhotic patients.

TABLE 14: CDR REANALYSIS (G2 TE NON-RESPONDERS OR RELAPSE OR BREAKTHROUGH): ICURS FOR SOFOSBUVIR VERSUS COMPARATORS

		Base-Case Analysis Submitted by Manufacturer	CDR Analysis A SK costs, utility increment (0.07), 80-Years Time Horizon and Lower Cost of Anemia	CDR Analysis B Analysis A + Lower Bound of the 95% CI for SOF SVR + Upper Bound of the 95% CI for Peg-INF/RBV SVR
ICUR SOF vs. no treatment				
Non-cirrhotic	Non-responders	$21,509	$28,594	$61,564
	Relapse or breakthrough	$17,765	$23,825	$31,413
Cirrhotic	Non-responders	Dominated	Dominated	Dominated
	Relapse or breakthrough	$2,999	$3,914	$23,944
ICUR SOF vs. Peg-INF/RBV				
Non-cirrhotic	Non-responders	$16,446	$16,941	$136,936
	Relapse or breakthrough	$12,323	$22,191	$31,487
Cirrhotic	Non-responders	Dominated	Dominated	Dominated
	Relapse or breakthrough	Dominates	$183	$62,162

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; N/A = not applicable; Peg-INF/RBV = pegylated interferon plus ribavirin; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced.

Genotype 3 Treatment-Naïve Interferon- Ineligible or Unwilling and Treatment-Experienced Interferon-Intolerant Non-cirrhotic and Cirrhotic Patients

Similar to the genotype 2 population, the number of genotype 3 patients in the sofosbuvir group who were intolerant to Peg-INF/RBV was small (n = 8). The SVR rate in non-cirrhotic patients was 100%, which is higher than that reported for ineligible or unwilling patients (66.7%). The POSITRON study did not conclude that patients ineligible or unwilling to receive Peg-INF/RBV had a lower response than intolerant patients. In fact, the Discussion of the POSITRON Clinical Study Report notes that, "However, in this study, the response rate in the ineligible and intolerant population was similar to the overall population.[26]

For this reason, the analysis in interferon-intolerant patients presented by the manufacturer was considered too uncertain, and CDR considered that the analysis in genotype 2 treatment-naive ineligible or unwilling patients is a better representation of the cost-effectiveness of sofosbuvir compared with no treatment in patients in whom Peg-INF/RBV is not an option.

In addition to the changes presented earlier, to account for uncertainty in SVR rates, the lower bound of the 95% confidence interval was applied, consistent with the manufacturer's deterministic sensitivity analyses (Table 15). ICURs for sofosbuvir versus no treatment were above $75,000 per QALY, in both non-cirrhotic and cirrhotic patients.

TABLE 15: CDR REANALYSIS (G3 TN INF-INELIGIBLE OR TE INF-INTOLERANT): ICURS FOR SOFOSBUVIR VERSUS NO TREATMENT

		Base-Case Analysis Submitted by Manufacturer	CDR Analysis A SK Costs, Utility Increment (0.07), 80-Years Time Horizon and Lower Cost of Anemia	CDR Analysis B Analysis A + Lower Bound of the 95% CI for SVR SOF
Non-cirrhotic	INF-ineligible or unwilling	$41,935	$55,864	$75,229
	INF-intolerant	$24,536	N/A	N/A
Cirrhotic	INF-ineligible or unwilling	$52,125	63,706	$102,612[a]
	INF-intolerant	$58,571	N/A	N/A

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; INF=interferon; N/A = not applicable; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive.
[a]The manufacturer used a 25.3% value for the lower bound of the 95% CI in its deterministic sensitivity analyses included in the Excel health economic model, but the point estimate is 22.2%. CDR assumed a lower bound of 15.3%.

Genotype 3 Treatment-Experienced Interferon Non-responders or Relapse or Breakthrough Non-cirrhotic and Cirrhotic Patients

Similar to the genotype 2 population, even if the number of non-responders was small in FUSION (sofosbuvir group: n = 12 for non-cirrhotic patients, n = 5 for cirrhotic patients), both populations were considered separately in the CDR reanalyses.

In addition to the changes presented earlier, to account for uncertainty in SVR rates, in a conservative scenario, the lower bound of the 95% CI for sofosbuvir SVR rates and upper bound of the 95% CI for Peg-INF/RBV SVR rates were applied, based on values provided in the manufacturer's deterministic sensitivity analyses (Table 2).

Results of the CDR reanalyses are presented in Table 16. In genotype 3 prior-relapse or breakthrough patients, sofosbuvir was not cost-effective versus no treatment and versus Peg-INF/RBV in non-cirrhotic patients. However, in cirrhotic patients, sofosbuvir was economically attractive versus no treatment and Peg-INF/RBV. In genotype 3 prior non-responders, compared with no treatment and Peg-INF/RBV, sofosbuvir was either dominated, or had ICURs above $150,000 per QALY.

TABLE 16: CDR REANALYSIS (G3 TE NON-RESPONDERS OR RELAPSE OR BREAKTHROUGH): ICURS FOR SOFOSBUVIR VERSUS COMPARATORS

		Base-Case Analysis Submitted by Manufacturer	CDR Analysis A SK Costs, Utility Increment (0.07), 80-Years Time Horizon and Lower Cost Of Anemia	CDR Analysis B Analysis A + Lower Bound of the 95% CI for SVR SOF
ICUR SOF vs. no treatment				
Non-cirrhotic	Non-responders	$50,346	$65,424	$152,190
	Relapse or breakthrough	$44,831	$58,318	$152,190
Cirrhotic	Non-responders	$23,709	28,962	$436,769
	Relapse or breakthrough	$9,573	$11,870	$27,902
ICUR SOF vs. Peg-INF/RBV				
Non-cirrhotic	Non-responders	$62,693	$80,783	dominated
	Relapse or breakthrough	$51,519	$66,811	dominated
Cirrhotic	Non-responders	$22,652	28,260	dominated
	Relapse or breakthrough	$5,777	$7,411	$30,657

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; N/A = not applicable; SK = Saskatchewan Formulary; Peg-INF/RBV = pegylated interferon plus ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced.

Genotype 3: Impact of Treatment Duration

The product monograph indicates that consideration should be given to extending the duration of therapy beyond 16 weeks and up to 24 weeks, guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history). The latest EASL guidelines[16] recommend that, if used with ribavirin only, a 24-week course of sofosbuvir should be used in genotype 3 patients (12 weeks if used in combination with Peg-INF/RBV). These are based on the results of the VALENCE trial,[15] which suggests that genotype 3 patients may benefit from a longer duration of sofosbuvir plus ribavirin (up to 24 weeks).

The impact of a longer course of treatment was not assessed in the economic model. CDR explored the potential impact of a 24-week course of sofosbuvir, using the genotype 3 non-cirrhotic patients INF-ineligible population (largest sample size). In the first scenario, treatment cost was modified to [redacted] and the SVR observed in the treatment-naive non-cirrhotic population from VALENCE was applied (94%). In the second scenario, which was more conservative, only the cost of treatment was modified, and it was assumed that the SVR would be the same as the one observed at 16 weeks (SVR = 66.7%; Table 17).

TABLE 17: CDR REANALYSIS (G3 TN INF- INELIGIBLE: IMPACT OF TREATMENT DURATION): ICURS FOR SOFOSBUVIR VERSUS NO TREATMENT

		Base-Case Analysis Submitted by Manufacturer	CDR Analysis A SK costs, Utility Increment (0.07), 80-Years Time Horizon and Lower Cost of Anemia Tx duration 24 weeks + Tx cost [redacted] SOF SVR 94%	CDR Analysis B (Analysis A with SOF SVR 66.7%)
Non-cirrhotic	INF-ineligible or unwilling	$41,935	$58,007	$86,045

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; INF=interferon; N/A = not applicable; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response; TN = treatment-naive; Tx = treatment.

Reanalysis Based on Price Reduction

Considering that CDR noted areas of uncertainty in the ICURs for each subgroup population, the potential impact of reducing the price of sofosbuvir was explored. Genotype 3 prior non-responder patients were considered to be of particular interest, as they are not likely to receive a second course of Peg-INF/RBV, and thus, sofosbuvir would currently be the only treatment alternative for that population. However, there is considerable uncertainty regarding the ICUR of sofosbuvir compared with no treatment because of the small sample size of genotype 3 non-responders in FUSION, which is reflected by the wide CI generated (27.7% to 84.8%), as well as potential for these patients to be candidates for a longer course of treatment; i.e., 24 weeks instead of 16 weeks.

TABLE 18: CDR ANALYSIS OF ICURS FOR SOFOSBUVIR VERSUS NO TREATMENT BASED ON VARIOUS PRICE REDUCTION SCENARIOS (G3 NON-CIRRHOTIC NON-RESPONDERS)

Scenario	ICUR Based on Manufacturer's Analysis Non-responders	CDR Analysis SK Costs, Utility Increment (0.07), 80-Years Time Horizon, Lower Cost of Anemia Lower Bound of the 95% CI for SVR SOF (27.7%)
Manufacturer's base case [redacted]	$50,346	$152,190
10% price reduction [redacted]	$44,916	$137,184
20% price reduction [redacted]	$39,487	$122,181
30% price reduction [redacted]	$34,058	$107,177
40% price reduction [redacted]	$28,628	$92,170
50% price reduction [redacted]	$23,199	$77,169
60% price reduction [redacted]	$17,769	$62,162
70% price reduction [redacted]	$12,340	$47,159
80% price reduction [redacted]	$6,911	$32,155
90% price reduction [redacted]	$1,481	$17,151

CDR = Common Drug Review; CI = confidence interval; G = genotype; ICUR = incremental cost-utility ratio; N/A = not applicable; SK = Saskatchewan Formulary; SOF = sofosbuvir; SVR = sustained virologic response.

4. DISCUSSION

The manufacturer submitted a CUA comparing sofosbuvir, telaprevir, boceprevir, Peg-INF/RBV, and no treatment, depending on the usual treatment by the selected subgroup populations genotype 1, genotype 2, and genotype 3. For the base-case analysis, comparative SVR and specific adverse events (anemia, rash, depression) rates were derived from individual clinical trials.

Clinical trials should be cautiously interpreted with regard to the limitation identified. The design of NEUTRINO (single-arm) and FUSION (double-arm) required use of historical controls and unadjusted indirect comparisons, which generates uncertainty in the ICURs. Furthermore, many of the comparisons were based on very small sample sizes and results in some subgroups were not consistent with overall findings from FUSION and POSITRON; e.g., cirrhotic patients presenting better SVR rates than non-cirrhotic patients, or intolerant patients presenting better SVR rates than ineligible patients.

The alternate analysis for genotype 1 treatment-naive non-cirrhotic patients based on the NMA was methodologically more appropriate, but still had some limitations; as noted in Appendix 7 of the CDR clinical review report, and the wide 95% CrI for odds ratios, sofosbuvir cost-effectiveness estimates could be worse than estimated by the manufacturer; conservative scenarios lead to sofosbuvir being dominated by boceprevir and telaprevir. Furthermore, the design of the model did not allow a probabilistic sensitivity analysis, which would allow for comparison of all treatment options simultaneously (for treatment-naive patients).

The manufacturer acknowledged the model assumptions and limitations with regard to the following factors:[9]

- NEUTRINO study for sofosbuvir genotype 1 treatment-naive patients did not use an active comparator, and consequently, clinical efficacy inputs for each of the comparators were retrieved from different trials.
- The model uses a high degree of granularity; appropriate data were not always available for each of the comparators and some subgroups' results were based on small numbers of patients. For example, sofosbuvir SVR inputs were based on 15 patients or fewer for many subgroups (genotype 2 and genotype 3 treatment-naive interferon-ineligible cirrhotic patients, and genotype 2 and genotype 3 treatment-experienced interferon-intolerant cirrhotic and non-cirrhotic patients).
- There was no possibility of CHC patients achieving spontaneous SVR.

The key limitations associated with the manufacturer's submission are summarized in Table 19.

In genotypes 2 and 3, the analysis in patients intolerant to interferon was considered too uncertain, given that it was based on a very small number of patients, and SVR rates were not consistent with overall findings from POSITRON, which concluded that the response rate in the ineligible and intolerant population was similar to the overall population.

TABLE 19: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Comparative efficacy (SVR rates) of SOF vs. TEL, BOC, Peg-INF/RBV for G1 TN: base-case analysis	No comparator group in NEUTRINO, the comparative SVR rates are based on an unadjusted indirect comparison (randomization is broken)	Uncertainty in the comparative effectiveness of SOF with TEL, BOC, and Peg-INF/RBV Potential overestimation of the SOF efficacy
NMA results reflect comparative SVR rates of agents in G1 TN non-cirrhotic patients	Wide CrI in the NMA results SOF trial included in the NMA used a 24-week regimen	Uncertainty in the comparative effectiveness of SOF with TEL, BOC, and Peg-INF/RBV Potential overestimation of the SOF efficacy
High degree of granularity in the HE model	Efficacy data for some of these subgroups are based on very small sample sizes	Potential overestimation of effectiveness of SOF Uncertainty in the ICURs generated in many of the subgroups
Duration of therapy in G3 patients	The model considers only a 16-week duration, while the product monograph and VALENCE trial indicate some patients will require 24 weeks. The proportion of patients who will receive a 24-week duration is unknown	Underestimation of SOF costs, and incidence of adverse events (incidence of adverse events will increase if treatment duration increases)
Disutility associated with treatment, utility increment in patients achieving SVR	Lack of good comparative quality-of-life data	Uncertainty in utility values and consequently in QALY estimations
Lack of good comparative data to assess adverse events profile for each comparator	For G1 TN patients, no comparator group in NEUTRINO; AEs not assessed in the NMA and taken from the product monographs instead of directly from clinical trials. Potential difference in reporting and severity of AEs was not considered. For G2 and G3 TE, FUSION did not have a control group	Potential overestimation of the incidence (and associated costs) of AEs with TEL and BOC
Price of TEL and BOC	The analysis did not consider potential price reduction with other DAAs	Price reductions for other DAAs will increase the ICUR of SOF
Lack of stratification based on patients' fibrosis stage	Patients with F0-F1-F2-F3 are all grouped in the same category. It is impossible to assess comparative cost-effectiveness for early stage disease (F0-F1)	Unknown

AE = adverse event; BOC = boceprevir; CrI = credible interval; DAA = direct-acting antiviral agent; F = fibrosis stage; G = genotype; HE = health economic; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; OR = odds ratio; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive.

To address uncertainty, CDR reviewers performed several additional sensitivity analyses in each of the selected populations. As SVR rates are a major source of variability, conservative estimates based on the 95% CI limits were used. In addition, considering the lack of good comparative quality-of-life data, more conservative assumptions were used with regard to utility values, particularly the utility increment for patients achieving SVR. Moreover, lifetime horizon was modified to 80 years of age (instead of 100 years of age) and costs associated with treatment-related anemia were lowered.

Other factors contribute to the uncertainty of cost-effectiveness of sofosbuvir but have not been quantified, such as monitoring costs and treatment durations. For example, the VALENCE study[15] demonstrated that in the genotype 3 population, patients would benefit from a 24-week regimen of sofosbuvir plus ribavirin. Although the impact of different treatment durations was assessed by CDR in the sensitivity analyses, it is not possible to know what proportion of genotype 3 patients will need 24 weeks of treatment, and whether the SVR rate observed in VALENCE would apply across all subgroups of genotype 3 patients.

Other incremental cost-effectiveness ratios, such as cost per avoided transplant, cost per avoided cirrhosis, and cost per avoided deaths, were presented by the manufacturer but should be considered as hypothesis-generating. None of the sofosbuvir studies was designed to assess these long-term outcomes.

4.1 Issues for Consideration

- The manufacturer is requesting listing in genotype 2 and 3 CHC patients for whom interferon is medically contraindicated. POSITRON was the only trial that included this population. Of the patients considered “ineligible” in POSITRON, most of them (57%) had a psychiatric disease. POSITRON also included patients in whom interferon was not necessarily contraindicated (i.e., they were unwilling patients). The definition of what constitutes an absolute contraindication to interferon may vary depending on clinical experts.
- The field of CHC is rapidly evolving. The cost-effectiveness of sofosbuvir used for longer periods or in combination with Peg-INF/RBV in genotype 3, or used in combination with other DAAs, is unknown.

4.2 Patient Input

Five patient groups representing people with HCV provided input. Patients believe sofosbuvir addresses a large gap and unmet patient need. It offers advantages due to its shorter treatment duration (12 to 24 weeks), easier administration (oral, once-daily dosing), decreased side effects compared with boceprevir and telaprevir, an interferon-free option for genotypes 2 and 3, and effectiveness in patients who have failed or who have relapsed on standard treatment. Adverse effects were not included in the manufacturer-funded NMA. Although the model included common adverse events (anemia, depression, rash), there is a lack of good comparative data. Rates of adverse events used in the health economic model were taken from product monographs, and the manufacturer does not seem to have accounted for severity of adverse events. Potential lower costs associated with a lower incidence of AEs, or lower incidence of long-term liver complication (e.g., liver transplant) with sofosbuvir are not sufficient to offset the higher drug cost of sofosbuvir compared with other DAAS.

5. CONCLUSIONS

The ICURs of sofosbuvir versus appropriate comparators varied widely across genotypes and various subgroups. Analyses in genotype 1 patients were limited by lack of direct comparative data. Most of the analyses in genotype 2 and genotype 3 patients were limited by the small sample size of the clinical trials used to inform efficacy inputs. Based on CDR reanalyses, sofosbuvir is likely cost-effective in the following subgroups: genotype 1 treatment-naive cirrhotic patients (compared with boceprevir and Peg-INF/RBV, but analyses were based on very small subgroups, and on a naive indirect treatment comparison); genotype 2 Peg-INF/RBV-ineligible and prior-relapsers or breakthrough (except cirrhotic patients) compared with no treatment and Peg-INF/RBV; genotype 3 prior-relapsers or breakthrough with cirrhosis, compared with no treatment and Peg-INF/RBV.

APPENDIX 1: COST COMPARISON TABLE

Clinical experts have deemed the comparators presented in Table 20 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 20: COST COMPARISON TABLE FOR DRUGS FOR CHRONIC HEPATITIS C

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost For 1 Course of Therapy ($)
Sofosbuvir (Sovaldi)	**400 mg**	**Tab**	[redacted][a]	**400 mg once daily**	**12 to 24 weeks[b]**	[redacted] **to** [redacted]
HCV Protease Inhibitor						
Boceprevir (Victrelis)	200 mg	Cap	12.5000	4 x 200 mg three times daily	24 to 44 weeks	25,200 to 46,200
Simeprevir (Galexos)	150 mg	Cap	471.4868[c]	150 mg once daily	12 weeks	39,605
Telaprevir (Incivek)	375 mg	Tab	69.3810	3 x 375 mg two times daily	12 weeks	34,968
Combination HCV Protease Inhibitor Plus Pegylated Interferon Alpha Plus Ribavirin Therapy						
Boceprevir plus Peg-INF-alpha-2b/RBV (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 Caps+ 2 Pens+ 56 Caps	2652.55[d] 2652.55[d] 2726.00[d] 2726.00[d]	Boceprevir 800 mg three times daily; Peg- INF 1.5 mcg/kg/week; RBV 800 to 1,400 per day	24 to 44 weeks	31,831 to 59,972
Combination Pegylated Interferon Alpha Plus Ribavirin[e] Therapy						
Peg-INF alpha-2a plus RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe/ 28 Tabs 35 Tabs 42 Tabs	395.8400	Peg- INF 180 mcg/week; RBV 800 to 1,200 mg/day[f]	24 to 48 weeks	9,500 to 19,000
Peg-INF alpha-2b plus RBV (Pegetron)	50 mcg/200 mg	2 Vials + 56 Caps	774.7700	Peg-INF 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day[f]	24 to 48 weeks	9,297 to 18,594
	150 mcg/200 mg	2 Vials + 84 or 98 Caps	856.1200			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 774.7700 856.1200 856.1200			9,297 to 20,547

HCV = hepatitis C virus; INF = interferon; IM = intramuscular; IU = international unit; IV = intravenous; peg-INF = pegylated interferon; RBV = ribavirin.

Source: Saskatchewan Drug Benefit (May 2014) prices unless otherwise stated.

[a]Manufacturer's submitted price.

[b]12 weeks for genotype 1, 2 and 4; 16 to 24 weeks for genotype 3.

[c]McKesson Canada (May 2014); includes mark-up.

[d]Quebec Provincial Drug Formulary (May 2014).

[e]Ribavirin was not available as a stand-alone drug at the time of the review.[f] Dosing varies by weight and HCV genotype.

APPENDIX 2: ADDITIONAL RESULTS FROM MANUFACTURER'S BASE-CASE AND SENSITIVITY ANALYSES

TABLE 21: MANUFACTURER'S FORECASTED CUMULATIVE INCIDENCE OF LIVER COMPLICATIONS, SVR PROBABILITIES, LIFE-YEARS GAINED AND QALY GAINED, OVER LIFETIME BY SELECTED STUDY POPULATIONS

Outcome	SOF+Peg-INF/RBV	TEL+Peg-INF/RBV	BOC+Peg-INF/RBV	Peg-INF/RBV	No treatment
G1, TN, non-cirrhotic patients					
Probability of SVR	91%	78%	70%	44%	N/A
No. cirrhosis cases/10,000	419	1,047	1,445	2,640	N/A
No. HCC cases/10,000	55	138	191	347	N/A
No. liver transplants/10,000	18	45	62	112	N/A
LY gained	17.2	17.2	17.1	17	N/A
QALY gained	13.8	13.5	13.4	12.9	N/A
G1, TN, cirrhotic patients					
Probability of SVR	81%	62%	50%	24%	N/A
No. cirrhosis cases/10,000	1,230	2,438	3,167	4,776	N/A
No. HCC cases/10,000	531	1,054	1,370	2,068	N/A
No. liver transplants/10,000	190	378	492	747	N/A
LY gained	16.3	15.4	14.8	13.6	N/A
QALY gained	12.3	11.4	10.9	9.7	N/A
G2, TN, non-cirrhotic patients, INF-ineligible					
Probability of SVR	92%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	512	N/A	N/A	N/A	6,148
No. HCC cases/10,000	69	N/A	N/A	N/A	821
No. liver transplants/10,000	22	N/A	N/A	N/A	269
LY gained	17.2	N/A	N/A	N/A	16.6
QALY gained	13.8	N/A	N/A	N/A	12.1
G2, TN, cirrhotic patients, INF-ineligible					
Probability of SVR	93%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	428	N/A	N/A	N/A	6,195
No. HCC cases/10,000	185	N/A	N/A	N/A	2,690
No. liver transplants/10,000	66	N/A	N/A	N/A	985
LY gained	17.0	N/A	N/A	N/A	12.3
QALY gained	12.9	N/A	N/A	N/A	8.5
G2, TE, non-cirrhotic patients, INF-intolerant					
Probability of SVR	100%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	0	N/A	N/A	N/A	6,148
No. HCC cases/10,000	0	N/A	N/A	N/A	821
No. liver transplants/ 10,000	0	N/A	N/A	N/A	269
LY gained	17.3	N/A	N/A	N/A	16.6
QALY gained	14.0	N/A	N/A	N/A	12.1

Outcome	SOF+Peg-INF/RBV	TEL+Peg-INF/RBV	BOC+Peg-INF/RBV	Peg-INF/RBV	No treatment
G2, TE, cirrhotic patients, INF-intolerant					
Probability of SVR	100%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	0	N/A	N/A	N/A	6,195
No. HCC cases/10,000	0	N/A	N/A	N/A	2,690
No. liver transplants/10,000	0	N/A	N/A	N/A	985
LY gained	17.3	N/A	N/A	N/A	12.3
QALY gained	13.3	N/A	N/A	N/A	8.5
G2, TE, INF non-responders, non-cirrhotic patients					
Probability of SVR	88%	N/A	N/A	25%	0%
No. cirrhosis cases/10,000	777	N/A	N/A	4,571	6,148
No. HCC cases/10,000	104	N/A	N/A	607	821
No. liver transplants/ 10,000	34	N/A	N/A	198	269
LY gained	17.2	N/A	N/A	16.8	16.6
QALY gained	13.7	N/A	N/A	12.5	12.1
G2, TE, INF non-responders, cirrhotic patients					
Probability of SVR	0%	N/A	N/A	19%	0%
No. cirrhosis cases/10,000	6,204	N/A	N/A	5,063	6,195
No. HCC cases/10,000	2,695	N/A	N/A	2,193	2,690
No. liver transplants/10,000	988	N/A	N/A	793	985
LY gained	12.2	N/A	N/A	13.4	12.3
QALY gained	8.4	N/A	N/A	9.5	8.5
G2, TE, relapsers or breakthrough, non-cirrhotic patients					
Probability of SVR	100%	N/A	N/A	25%	0%
No. cirrhosis cases/10,000	0	N/A	N/A	4,571	6,148
No. HCC cases/10,000	0	N/A	N/A	607	821
No. liver transplants/10,000	0	N/A	N/A	198	269
LY gained	17.3	N/A	N/A	16.8	16.6
QALY gained	14.0	N/A	N/A	12.5	12.1
G2, TE, relapsers or breakthrough, cirrhotic patients					
Probability of SVR	75%	N/A	N/A	19%	0%
No. cirrhosis cases/10,000	1,597	N/A	N/A	19%	6,195
No. HCC cases/10,000	690	N/A	N/A	5,063	2,690
No. liver transplants/10,000	247	N/A	N/A	2,193	985
LY gained	16.0	N/A	N/A	13.4	12.3
QALY gained	12.1	N/A	N/A	9.5	8.5
G3, TN, INF-ineligible, non-cirrhotic patients					
Probability of SVR	67%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	2,069	N/A	N/A	N/A	6,148
No. HCC cases/10,000	277	N/A	N/A	N/A	821
No. liver transplants/10,000	90	N/A	N/A	N/A	269
LY gained	17.1	N/A	N/A	N/A	16.6
QALY gained	13.3	N/A	N/A	N/A	12.1

Outcome	SOF+Peg-INF/RBV	TEL+Peg-INF/RBV	BOC+Peg-INF/RBV	Peg-INF/RBV	No treatment
G3, TN, INF-ineligible, cirrhotic patients					
Probability of SVR	22%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	4,884	N/A	N/A	N/A	6,195
No. HCC cases/10,000	2,117	N/A	N/A	N/A	2,690
No. liver transplants/10,000	768	N/A	N/A	N/A	985
LY gained	13.3	N/A	N/A	N/A	12.3
QALY gained	9.5	N/A	N/A	N/A	8.5
G3, TE, INF-intolerant, non-cirrhotic patients					
Probability of SVR	100%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	0	N/A	N/A	N/A	6,148
No. HCC cases/10,000	0	N/A	N/A	N/A	821
No. liver transplants/10,000	0	N/A	N/A	N/A	269
LY gained	17.3	N/A	N/A	N/A	16.6
QALY gained	14.0	N/A	N/A	N/A	12.1
G3, TE, INF-intolerant, cirrhotic patients					
Probability of SVR	20%	N/A	N/A	N/A	0%
No. cirrhosis cases/10,000	5,019	N/A	N/A	N/A	6,195
No. HCC cases/10,000	2,176	N/A	N/A	N/A	2,690
No. liver transplants/10,000	790	N/A	N/A	N/A	985
LY gained	13.2	N/A	N/A	N/A	12.3
QALY gained	9.4	N/A	N/A	N/A	8.5
G3, TE, INF non-responders, non-cirrhotic patients					
Probability of SVR	58%	N/A	N/A	25%	0%
No. cirrhosis cases/10,000	2,585	N/A	N/A	4,571	6,148
No. HCC cases/10,000	346	N/A	N/A	607	821
No. liver transplants/10,000	113	N/A	N/A	198	269
LY gained	17.0	N/A	N/A	16.8	16.6
QALY gained	13.2	N/A	N/A	12.5	12.1
G3, TE, INF non-responders, cirrhotic patients					
Probability of SVR	40%	N/A	N/A	10%	0%
No. cirrhosis cases/10,000	3,793	N/A	N/A	5,567	6,195
No. HCC cases/10,000	1,642	N/A	N/A	2,413	2,690
No. liver transplants/10,000	593	N/A	N/A	876	985
LY gained	14.2	N/A	N/A	13.0	12.3
QALY gained	10.4	N/A	N/A	9.1	8.5
G3, TE, relapsers or breakthrough, non-cirrhotic patients					
Probability of SVR	64%	N/A	N/A	25%	0%
No. cirrhosis cases/10,000	2,217	N/A	N/A	4,571	6,148
No. HCC cases/10,000	297	N/A	N/A	607	821
No. liver transplants/10,000	97	N/A	N/A	198	269
LY gained	17.0	N/A	N/A	16.8	16.6
QALY gained	13.3	N/A	N/A	12.5	12.1

Outcome	SOF+Peg-INF/RBV	TEL+Peg-INF/RBV	BOC+Peg-INF/RBV	Peg-INF/RBV	No treatment
G3, TE, relapsers or breakthrough, cirrhotic patients					
Probability of SVR	67%	N/A	N/A	10%	0%
No. cirrhosis cases/10,000	2,124	N/A	N/A	5,567	6,195
No. HCC cases/10,000	918	N/A	N/A	2,413	2,690
No. liver transplants/10,000	329	N/A	N/A	876	985
LY gained	15.6	N/A	N/A	13.0	12.3
QALY gained	11.7	N/A	N/A	9.1	8.5

BOC = boceprevir; G = genotype; HCC = hepatocellular carcinoma; INF = interferon; LY = life-years; N/A = not applicable; No. = number; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive.

TABLE 22: MANUFACTURER'S DETERMINISTIC AND PROBABILISTIC SENSITIVITY ANALYSES

Comparison	Deterministic Sensitivity Analyses		Probabilistic Sensitivity Analyses
	Parameters With the Largest Impact	ICUR ($/QALY) Range	Probability of SOF Being Cost-Effective at a 50,000$/QALY Threshold
G1 TN — non-cirrhotic patients			
SOF vs. Peg-INF/RBV	Utility: cirrhotic without treatment	$38,172	98%
SOF vs. TEL	SVR comparator	$10,397	99% (< $20,000/QALY)
SOF vs. BOC	SVR comparator	$22,151	98%
G1 TN — cirrhotic patients			
SOF vs. Peg-INF/RBV	Costs: cirrhotic disease SVR	$7,603	98%
SOF vs. TEL	All scenarios	Sofosbuvir dominates TEL	93% probability of SOF dominating TEL 99% probability of the ICER remaining under $20,000/QALY
SOF vs. BOC	SVR 24 comparator (cirrhotic)	$3,121	81% probability of SOF dominating BOC; 99% probability of the ICER remaining under $20,000/QALY
G2 TN — INF-ineligible non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$26,266	100%
G2 TN — INF-ineligible cirrhotic patients			
SOF vs. no treatment	Costs – cirrhotic disease – SVR	$6,114	99% (< $20,000/QALY)
G2 TE — INF-intolerant non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$23,793	100%

Comparison	Deterministic Sensitivity Analyses		Probabilistic Sensitivity Analyses
	Parameters With the Largest Impact	ICUR ($/QALY) Range	Probability of SOF Being Cost-Effective at a 50,000$/QALY Threshold
G2 TE — INF-intolerant cirrhotic patients			
SOF vs. no treatment	Sofosbuvir dominates in all scenarios except change in costs of other health states	$3,016	98% (< $20,000/QALY)
G2 TE — INF non-responders non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$28,803	98%
SOF vs. Peg-INF/RBV	Utility – cirrhotic without treatment	$21,728	97.3%
G2 TE — INF non-responders, cirrhotic patients			
SOF vs. no treatment	All scenarios	Sofosbuvir is dominated	0%
SOF vs. Peg-INF/RBV	All scenarios	Sofosbuvir is dominated	0%
G2 TE — relapse or breakthrough, non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$23,793	100%
SOF vs. Peg-INF/RBV	Utility – cirrhotic without treatment	$16,321	100%
G2 TE — relapse or breakthrough, cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$11,431	99%
SOF vs. Peg-INF/RBV	Costs − cirrhotic disease SVR	$6,226	99%
G3 TN — INF-ineligible non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$56,134	72% (< $20,000/QALY)
G3 TN — INF-ineligible cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$192,582	42%
G3 TE — INF-intolerant non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$32,861	99%
G3 TE — INF-intolerant cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$215,294	34%
G3 TE — INF non-responders, non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$67,378	44%
SOF vs. PR	SVR 24 comparator	$86,792	32.7%

Comparison	Deterministic Sensitivity Analyses		Probabilistic Sensitivity Analyses
	Parameters With the Largest Impact	ICUR ($/QALY) Range	Probability of SOF Being Cost-Effective at a 50,000$/QALY Threshold
G3 TE — INF non-responders cirrhotic patients			
SOF vs. no treatment	Utility –cirrhotic without treatment	$89,358	73%
SOF vs. Peg-INF/RBV	Utility – cirrhotic without treatment	$78,499	64.5%
G3 TE — relapse or breakthrough non-cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$60,007	60%
SOF vs. Peg-INF/RBV	SVR 24 comparator (non-cirrhotic)	$68,086	44.5%
G3 TE — relapse or breakthrough cirrhotic patients			
SOF vs. no treatment	Utility – cirrhotic without treatment	$36,429	97%
SOF vs. Peg-INF/RBV	Utility – cirrhotic without treatment	$21,105	98.2%

BOC = boceprevir; G = genotype; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; INF = interferon; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive.

APPENDIX 3: SUMMARY TABLE OF COMMON DRUG REVIEW REANALYSES

Subgroups	ICURs ($/QALY)			
	SOF vs. NT	SOF vs. Peg-INF/RBV	SOF vs. TEL	SOF vs. BOC
G1 TN — non-cirrhotic patients	N/A	Best available estimate $50,266 Worst case: 135,391	Best available estimate $11,531 Worst case: SOF dominated	Best available estimate $14,030 Worst case: SOF dominated
G1 TN — cirrhotic patients	N/A	Best available estimate $7,119	Best available estimate SOF dominates Worst case: SOF dominated	Best available estimate SOF dominates Worst case: $3,237
G2 TN — INF-ineligible non-cirrhotic patients	$28,983			
G2 TN — INF-ineligible cirrhotic patients	$3,268			
G2 TE — INF-intolerant non-cirrhotic patients	N/A			
G2 TE — INF-intolerant cirrhotic patients	N/A			
G2 TE — INF non-responders, non-cirrhotic patients	$61,564	$136,936		
G2 TE — INF non-responders cirrhotic patients	SOF dominated	SOF dominated		
G2 TE — relapse or breakthrough non-cirrhotic patients	$31,413	$31,487		
G2 TE — relapse or breakthrough cirrhotic patients	$23,944	$62,162		
G3 TN — INF-ineligible non-cirrhotic patients	$75,229			
G3 TN — INF-ineligible cirrhotic patients	$102,612			
G3 TE — INF-intolerant non-cirrhotic patients	N/A			
G3 TE — INF-intolerant cirrhotic patients	N/A			
G3 TE — INF non-responders, non-cirrhotic patients	$152,190	SOF dominated		
G3 TE — INF non-responders cirrhotic patients	$436,769	SOF dominated		

Subgroups	ICURs ($/QALY)			
	SOF vs. NT	SOF vs. Peg-INF/RBV	SOF vs. TEL	SOF vs. BOC
G3 TE — relapse or breakthrough non-cirrhotic patients	$152,190	SOF dominated		
G3 TE — relapse or breakthrough cirrhotic patients	$27,902	$30,657		

BOC = boceprevir; CDR = Common Drug Review; G = genotype; ICUR = incremental cost-utility ratio; INF = interferon; N/A = not applicable; NT = no treatment; Peg-INF/RBV = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 23: 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 • CIs around SVR rates used for the deterministic sensitivity analyses were not included in the report and had to be traced from the Excel model.			
Was the submission well organized and was information easy to locate?	X		
Comments • CDR noted that TN was inverted with TE in a few places in the report (e.g., abbreviations list)			

CDR = Common Drug Review; CI = confidence interval; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naive.

TABLE 24: AUTHOR INFORMATION

Authors	Affiliations		
Canadian model adaptation: Axia Research			
	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		

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