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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR (VOSEVI)

(Gilead Sciences Canada, Inc.)

Indication: Hepatitis C infection genotype 1 to 6

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

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Abbreviations

CC	compensated cirrhosis
CHC	chronic hepatitis C
DAA	direct-acting antiviral
DCC	decompensated cirrhosis
GT	genotype
HCC	hepatocellular carcinoma
ICUR	incremental cost-utility ratio
NC	non-cirrhotic
NT	no treatment
PR	pegylated interferon plus ribavirin
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RBV	ribavirin
SOF	sofosbuvir
SVR	sustained virologic response
VEL	velpatasvir
VOX	voxilaprevir

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)
Study Question	To conduct a cost-utility analysis of SOF/VEL/VOX versus appropriate comparators, from a health care system perspective, for the treatment of chronic hepatitis C virus (HCV) infection in adult patients without cirrhosis or with compensated cirrhosis who have: • genotype (GT) 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an NS5A inhibitor; or • GT-1, 2, 3, or 4 infection and have been previously treated with a regimen containing SOF without an NS5A inhibitor.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with chronic HCV infection • GT1-6 NS5A experienced • GT1-4 NS5A naive but previously treated with a regimen containing SOF
Treatment	SOF/VEL/VOX for 12 weeks (cirrhotic and non-cirrhotic)
Outcome(s)	Quality-Adjusted Life-Years (QALYs)

Comparator(s)	• NS5A naive:
	  ○ SOF/VEL for 12 weeks
	  ○ No treatment
	• NS5A experienced
	  ○ No treatment

Perspective	Canadian public payer
Time Horizon	Lifetime (to 80 years of age)

Results for Base Case	The incremental cost-utility ratios (ICURs) by subgroup were as follows:
	• NS5A-naive non-cirrhotic
	  ○ SOF/VEL/VOX vs. SOF/VEL: SOF/VEL/VOX dominant (higher QALY gains and lower overall costs)
	  ○ SOF/VEL/VOX vs. no treatment: $6,254 per QALY
	• NS5A-naive cirrhotic
	  ○ SOF/VEL/VOX vs. SOF/VEL: SOF/VEL/VOX dominant (higher QALY gains and lower overall costs)
	  ○ SOF/VEL/VOX vs. no treatment: $11,638 per QALY
	• NS5A-experienced non-cirrhotic
	  ○ SOF/VEL/VOX vs. no treatment: $6,078 per QALY
	• NS5A-experienced cirrhotic
	  ○ SOF/VEL/VOX vs. no treatment: $12,159 per QALY.

Key Limitations	• The manufacturer combined all genotypes together in the base case. Analysis by genotype was only provided for GT3 and non-GT3. • The sample size of many subgroups with reported 100% sustained virologic response rates was small, and uncertainty in these estimates was not accounted for appropriately. • Costs for hepatocellular carcinoma health states appear unrealistic and much higher than in the recent CADTH Therapeutic Review for chronic hepatitis C drugs.

CDR Estimate(s)	• Most identified limitations could not be addressed by CDR, either because of the model structure or lack of clinical information, and those that could were generally of lesser importance.
	• Based on CDR reanalyses accounting only for costs assigned to hepatocellular carcinoma HCC states, the findings were as follows:
	  ○ In patients who were non-cirrhotic, SOF/VEL/VOX resulted the following ICURs:
	  ▪ $7,520 per QALY compared with no treatment in patients who are NS5A experienced
	  ▪ $7,696 per QALY compared with no treatment in patients who are NS5A naive. SOF/VEL/VOX dominates SOF/VEL in patients who are NS5A naive (resulting in higher QALY gains and lower overall costs compared with SOF/VEL).
	  ○ In patients who were cirrhotic, SOF/VEL/VOX resulted in the following ICURs:
	  ▪ $17,384 per QALY compared with no treatment in patients who are NS5A experienced
	  ▪ $16,864 per QALY compared with no treatment in patients who are NS5A naive
	  ▪ $923 per QALY when compared with SOF/VEL in patients who are NS5A naive.

Drug	Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
Indication	For the treatment of chronic hepatitis C virus (HCV) infection in adult patients without cirrhosis or with compensated cirrhosis who have • genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor; or • genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
Reimbursement Request	As per indication
NOC Date	16 August 2017
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Background

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi) is a single tablet that combines sofosbuvir with velpatasvir and voxilaprevir. It is recommended as a 12-week, single-tablet regimen for the treatment of chronic hepatitis C virus (HCV) infection for patients without cirrhosis or with compensated cirrhosis.[1] The manufacturer submitted a price of $714.29 per tablet, or $60,000 for a 12-week course.[2]

The manufacturer submitted a cost-utility analysis based on a Markov cohort model, where patients start in health states representing initial METAVIR scores (a scoring system used to assess the extent of inflammation and stage of fibrosis or scarring in patients with hepatitis C) with active chronic hepatitis C (CHC) infection, sustained virologic response (SVR) states, distal consequences of HCV infection, and death.[3] The manufacturer presents results in the NS5A-naive and NS5A-experienced populations, each of which was stratified by cirrhosis status. The comparators considered were no treatment (both populations) and treatment with SOF/VEL (in NS5A-naive patients only). The SVR rates for SOF/VEL/VOX were based on the POLARIS trials,[4] which established SVR rates of more than 96% in both NS5A-experienced (versus placebo, POLARIS-1) and NS5A-naive (versus SOF/VEL, POLARIS-4) patients.

The manufacturer's results suggest that SOF/VEL/VOX is a cost-effective treatment option in patients with CHC with genotypes (GTs) 1 to 6 who are NS5A experienced as well as in GT1-4 patients who are NS5A naive, with SOF/VEL/VOX dominating SOF/VEL (i.e., offering higher quality-adjusted life-year (QALY) gains and lower overall costs) and associated with an incremental cost-utility ratio (ICUR) of $12,000 per QALY compared with no treatment or SOF/VEL. Results were similar between the GT3 and non-GT3 populations for SOF/VEL/VOX compared with no treatment or SOF/VEL.

Summary of Identified Limitations and Key Results

CDR identified a number of issues with the manufacturer's pharmacoeconomic submission. The manufacturer's model combined all genotypes together in the base case with only an option to examine results by GT3 versus non-GT3 patients. The model does not include

options to generate the results according to genotype (other than for GT3) or according to cirrhotic and non-cirrhotic subgroups within any genotype except for GT3.

There were also issues with the quality of the clinical evidence. The effectiveness parameters of the model were drawn from very little data for a number of the subgroups considered by the manufacturer, as the POLARIS trials captured primarily GT1 and GT3 patients. The little data for other subgroups is to be expected, as the prevalence of these viral variants is globally low.[5] Another limitation was that the costs assigned to hepatocellular carcinoma (HCC) health states were much higher than in the recent CADTH Therapeutic Review.[6]

Due to the design of the submitted model and a lack of clinical information, CDR could only conduct a reanalysis whereby the costs assigned to HCC states were consistent with the CADTH Therapeutic Review. The results of the CDR reanalysis did not impact the manufacturer's base case results for non-cirrhotic patients, but in the cirrhotic group, SOF/VEL/VOX was no longer dominant when compared with SOF/VEL and resulted in an incremental cost-utility ratio of $923 per QALY.

Conclusions

The key limitations of the submitted economic analysis, as identified by CDR, were the use of a model that combines all genotypes and the uncertainty of clinical efficacy parameters (with clinical information largely representative of GT1 and GT3 and small populations for other genotypes). As such, results were presented for overall CHC (GT1 through GT6), and GT3 and non-GT3.

The availability of clinical efficacy data for SOF/VEL/VOX in patients with genotypes other than 1 or 3 (i.e., GT2, 4, 5, and 6) continues to present a challenge for this and other CDR reviews on treatment for CHC; this is especially true for GT5 and GT6, as the prevalence in most regions is low. Therefore, cautious consideration is warranted when interpreting the overall results of SOF/VEL/VOX for genotypes 2, 4, 5, and 6.

CDR was only capable of conducting a reanalysis that changed the costs associated with the HCC health state in the model.

At the submitted price of $714.29 per tablet, SOF/VEL/VOX is similarly priced to SOF/VEL. Based on the POLARIS-4 trial, SOF/VEL/VOX for 12 weeks appears be associated with higher SVR rates 12 weeks after the end of treatment compared with SOF/VEL. Although patients recruited in POLARIS-4 included those with experience with direct-acting antivirals with genotypes 1, 2, 3, or 4 chronic HCV infection who have not received an NS5A inhibitor, the trial mostly captured patients with either GT1 or GT3, which limits the generalizability of the trial's results for the indicated population.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis using a Markov state transition model that consisted of nine states, with transitional probabilities describing the movement between the states.[3] Costs, utilities, and mortality were associated with each state. The model structure is shown in Figure 1. The model maintained different cirrhosis states: non-cirrhotic (NC]), with METAVIR fibrosis scores of F0-F3, and compensated cirrhosis (CC), with a METAVIR score of F4. The manufacturer noted that CC patients have worse outcomes in the nearer term and had lower sustained virologic response (SVR) rates with previous treatments. The manufacturer's model also permitted use of a blended NC/CC population. Results for a blended population depended on the proportion of CC to NC patients. In the default, the proportion was set at that observed in the POLARIS trials.[4] However, no results were presented in the manufacturer's report for a blended CC/NC population.

The manufacturer compared SOF/VEL/VOX to no treatment and SOF/VEL in patients who had not previously received an NS5A inhibitor (i.e., NS5A naive) based on clinical information from the POLARIS-4 trial,[4] while SOF/VEL/VOX was only compared with no treatment in NS5A-experienced patients based on clinical information from the POLARIS-1 trial.[4]

Patients entered the model, were assigned treatment, and moved to the SVR health state after completing treatment if they had undetectable hepatitis C virus ribonucleic acid (HCV RNA) 12 weeks after the end of treatment. Patients who achieved SVR were considered to have permanently cleared the virus, with no spontaneous reactivation of the HCV infection or re-infection in the base case. NC patients had no risk of future hepatic sequelae from HCV. Cirrhotic patients with SVR continued to have cirrhosis, but with a reduced risk of progression to more severe health states. Patients without an SVR faced an annual probability of progressing from F0 through to F4, decompensated cirrhosis (DCC), and other outcomes as if they had not received antiviral treatment. Patients in the CC and DCC stages could progress to HCC. Patients with DCC or hepatocellular carcinoma (HCC) could progress to liver transplant. Following liver transplantation, patients had a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase, patients remained at a higher risk of death, as compared with the general population.

Age- and gender-specific general population mortality rates were applied to each health state in the model.[4] Additionally, excess hepatic mortality was assigned to patients in the last and most severe states (DCC, HCC, liver transplant, and post-liver transplantation) based on the CADTH Therapeutic Review on drugs for CHC infection.[6]

Many elements of the model follow the recent CADTH Therapeutic Review closely,[6] including the natural history and utility figures and some cost figures. Costs were broken down into drug costs, monitoring costs, adverse event costs, and health-state related costs. However, there was no clear breakdown in the submitted report for how these costs were computed.

The patient cohort is assumed to have a mean age of 58 at the start of the model and is followed up to 80 years of age similar to the POLARIS trials.[4] The perspective of the model

is that of the Canadian publicly funded health care system, with a base currency of 2017 Canadian dollars. A 1.5% discount rate was applied to both costs and quality-adjusted life-years (QALYs).

Manufacturer's Base Case

The manufacturer's main results are that SOF/VEL/VOX demonstrated high SVR rates compared with SOF/VEL and no treatment based on the POLARIS trials[4] and is priced in line with SOF/VEL. The manufacturer does not provide analyses comparing SOF/VEL/VOX against other comparators for individual genotypes (Table 2). Manufacturer sequential base case results according to cirrhosis status are presented in Table 15 in Appendix 3.

Table 2: Results of Manufacturer Base-Case Analysis for SOF/VEL/VOX

	Population/ Comparator	Total Costs ($)	Total QALYs	Incremental Cost per QALY
NS5A experienced	**Non-cirrhotic patients**			
	No treatment	$49,462	11.73	
	SOF/VEL/VOX	$63,253	14.00	$6,078
	Compensated cirrhosis patients			
	No treatment	$105,406	8.74	
	SOF/VEL/VOX	$151,001	12.49	$12,159
NS5A naive	**Non-cirrhotic patients**			
	Comparator: No treatment			
	No treatment	$49,462	11.73	
	SOF/VEL/VOX	$63,561	13.98	$6,254
	Comparator: SOF/VEL			
	SOF/VEL	$65,521	13.89	SOF/VEL/VOX dominates
	SOF/VEL/VOX	$63,561	13.98	
	Compensated cirrhosis patients			
	Comparator: No treatment			
	No treatment	$105,406	8.74	
	SOF/VEL/VOX	$150,471	12.61	$11,638
	Comparator: SOF/VEL			
	SOF/VEL	$152,359	12.17	SOF/VEL/VOX dominates
	SOF/VEL/VOX	$150,471	12.61	

Source: Manufacturer's pharmacoeconomic submission.[3]
ICUR = incremental cost-utility ratio; NS5A = nonstructural viral protein 5A; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

Summary of Manufacturer's Sensitivity Analyses

Deterministic Sensitivity Analyses

The deterministic sensitivity analyses reported by the manufacturer examined

- Separately varying SVR rates for SOF/VEL in GT3 CC patients based on the POLARIS-4 trial (SVR rates for SOF/VEL/VOX were similar in non-GT3 and GT3 patients)
- Applying a discount rate of 0 and 3%
- Varying the model time horizon.

Results of manufacturer's deterministic sensitivity analyses were robust and aligned with the base case results. The following changes were noted:

- The comparison versus no treatment in both NC patient populations had the most amount of variation, from dominance to $11,000/QALY.
- The differences between the GT3 and non-GT3 populations were modest for SOF/VEL/VOX and no treatment. Only SOF/VEL showed impact from GT3 versus non-GT3, and only in the CC population, due to its lower efficacy in these patients. However, this was considered irrelevant, as SOF/VEL/VOX dominated SOF/VEL even in non-GT3 patients.
- The results obtained from variation in discount rates and time horizons were only modestly different from the reference case.

Probabilistic Sensitivity Analyses

The probabilistic sensitivity analysis presented in the manufacturer's report applied beta and gamma distributions to "key variables," i.e., utility values and the utility increment due to SVR. Health-state costs were also varied, as well as monitoring costs and adverse event costs, but drug costs were not. Transition probabilities were also modified using beta distributions (although Dirichlet distributions are more appropriate where more than two outcomes can occur from a single state).

The results of the manufacturer's probabilistic sensitivity analysis found the results of the model to be robust, with near 100% probability of the base case results being cost-effective at thresholds of $20,000 and $50,000 per QALY gained in all four patient populations.

Limitations of Manufacturer's Submission

CDR identified a number of limitations with the submitted analyses. Unfortunately, a number of the issues are sufficiently fundamental to the analysis that they could not be remedied without a complete rebuild of the model, which was beyond the scope of the evaluation.

- Combined model. The manufacturer's model combined and considered all genotypes together in the base case, with only an option to examine results by GT3 versus non-GT3 patients. The model does not include separate options to generate the results according to genotype (other than for GT3) based on the clinical data available for each genotype and does it generate results according to cirrhotic and NC subgroups within the genotypes except for GT3.
- **Small sample sizes.** Within the model, assumption of 100% SVR from small sample sizes can be problematic when no allowance is made for uncertainty. Using these data as reported in POLARIS-1, the manufacturer treats the SVR for GT5 and GT6 treatment-

experienced patients with or without CC as 100% based on only one GT5 patient and six GT6 patients. For GT4 patients, the SVR of SOF/VEL/VOX is based on 19 patients in NS5A-naive patients and on 22 patients in the NS5A-experienced group. The extrapolation of overall results to populations with small patient sizes warrants cautious consideration. However, it is acknowledged that the prevalence of these viral variants (GT5 and GT6) as well as GT2 and GT4 in most regions is globally low.[5]

- **Treatment of HCC costs is inconsistent with CADTH Therapeutic Review.** In the manufacturer's base-case analysis, the annual costs associated with cirrhotic health states (DCC, HCC, and liver transplant) were derived from the CADTH Therapeutic Review from the patient age range of 45 to 54, while the manufacturer's model used an entry patient age of 58. In addition, the CADTH review states that the "late phase" begins with a diagnosis of DCC or HCC, or both, and has an annual cost of $14,954 (adjusted for 2017). In the manufacturer's model, the $14,954 value is used for the DCC state, but a different and higher figure of $42,847 is used for the HCC state.

CADTH Common Drug Review Reanalyses

- Many of the concerns detailed above could not be addressed, as they are driven by structural challenges with the model.
- **Treatment of HCC costs:** CDR conducted a reanalysis using the approach of the CADTH review; CDR utilized the annual costs from the CADTH Therapeutic Review for the age range of 55 to 64, and the costs per year for HCC were modified to be similar to those of DCC. The results of the CDR reanalysis did not significantly impact the manufacturer's base case results for NC patients, but in the cirrhotic group, SOF/VEL/VOX was not dominant over SOF/VEL and had resulted in an incremental cost-utility ratio of $923 per QALY.

Issues for Consideration

Glecaprevir/pibrentasvir (Maviret), indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with or without CC, including patients with HCV genotype 1 infection who were previously treated either with a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor (but not both classes of inhibitors), is currently being reviewed by CDR.[7]

Patient Input

Five patient groups submitted input for SOF/VEL/VOX: The Canadian Liver Foundation, the Canadian Treatment Action Council, Hepatitis C Education and Prevention Society, the Pacific Hepatitis C Network, and the Centre Associatif Polyvalent d'Aide Hépatite C.

According to patient group input received by CDR for this submission, symptoms of CHC infection vary widely, with some patients having few or no symptoms, and others experiencing fatigue, nausea, headaches, sensitivities to light and food, memory loss, mood swings, itchy skin, abdominal pain, severe joint and muscle pain, portal hypertension, sleeplessness, slowed reflexes, psoriasis, peripheral neuropathy, osteopenia, diarrhea, and muscle wasting. In some patients, the disease affects cognitive function and memory. Fatigue and other symptoms may be severe and can limit patients' ability to work, care for family members, and maintain friendships. The health states of the economic model capture the impact of such symptoms on quality of life to some extent, but they may not be reflective of the full spectrum of symptom severity experienced by patients in clinical practice.

Spouses and caregivers for patients with CHC infection are faced with a substantial burden, as the symptoms of CHC infection can leave the patient dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, their relationships, or the care of children. The submitted model only reflects costs to the health care system and clinical effects experienced by the patient.

Patient groups considered the adverse effects caused by direct-acting antiviral (DAA) regimens for CHC infection to be generally milder and more tolerable than those associated with pegylated interferon plus ribavirin. The submitted analysis did not incorporate disutilities due to adverse effects.

Patient group input also described the added challenges faced by patients with HIV/HCV coinfection, particularly with respect to more rapid progression of liver disease and the need to manage potential drug interactions between anti-HIV and anti-HCV medications. The submitted model did not permit estimation of the cost-effectiveness of SOF/VEL/VOX in patients co-infected with HIV. The POLARIS-1 and -4 trials had excluded patients with HIV coinfection as well.[4]

Conclusions

The key limitations of the submitted economic analysis, as identified by CDR, were the use of a model that combines all genotypes and uncertainty of clinical efficacy parameters (with clinical information largely representative of GT1 and GT3 infection, and small populations for other genotypes). As such, results were presented for overall CHC (GT1 through GT6), and GT3 and non-GT3. Further, the manufacturer did not specifically report the effects of treatment for patients with DCC; the model is based on the POLARIS-1 and -4 trials, and both trials had exclusion criteria for patients with DCC.

The availability of clinical efficacy data for SOF/VEL/VOX in patients with genotypes other than 1 or 3 (i.e., GT2, 4, 5, and 6) continues to present a challenge for this and other CDR reviews on treatment for CHC, and especially for GT5 and GT6, as the prevalence in most regions is low. Therefore, cautious consideration is warranted when interpreting the overall results of SOF/VEL/VOX for genotypes 2, 4, 5, and 6.

CDR was only capable of conducting a reanalysis that changed the costs associated with the HCC health state in the model.

At the submitted price of $714.29 per tablet, SOF/VEL/VOX is similarly priced to SOF/VEL. Based on the POLARIS-4 trial, SOF/VEL/VOX for 12 weeks appears be associated with higher SVR rates 12 weeks after the end of treatment compared with SOF/VEL. Although patients recruited in POLARIS-4 included those with experience with DAAs with genotypes 1, 2, 3, or 4 chronic HCV infection who had not received an NS5A inhibitor, the trial mostly captured patients with either GT1 or GT3 infection, which limits the generalizability of the trial's results for the indicated population.

Appendix 1: Cost Comparison

The comparators presented in the Table 3 have been deemed to be appropriate treatments for hepatitis C virus (HCV) by clinical experts, but not all are comparators of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in the Table 3 and, as such, may not represent the actual costs to public drug plans.

Table 3: CADTH Common Drug Review Cost Comparison Table for Drugs Indicated for HCV Genotype 1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	400 mg/ 100 mg/100 mg	Tablet	714.2857[a]	1 tablet daily	12 weeks	60,000	60,000
Interferon-free regimens							
Sofosbuvir/ velpatasvir (Epclusa)	400 mg/ 100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	60,000
Sofosbuvir/ velpatasvir (Epclusa) plus RBV	400 mg/ 100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[b]		3,045 to 3,654	
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	Tablet	714.2856[c]	300 mg/120 mg daily	8 weeks[d]	40,000	40,000
					12 weeks[e]	60,000	60,000
					16 weeks[f]	80,000	80,000
Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi)	60 mg	Tablet	428.5714	60 mg daily	12 weeks[g]	36,000	91,000
	400 mg	Tablet	654.7619	400 mg daily		55,000	
Daclatasvir (Daklinza) plus Asunaprevir (Sunvepra) *Genotype 1b*	60 mg	Tablet	428.5714	60 mg daily	24 weeks	72,000	85,000
	100 mg	Tablet	38.6905	100 mg twice daily		13,000	
Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) plus RBV	60 mg	Tablet	428.5714	60 mg daily	12 weeks[h]	36,000	94,045 to 94,654
	400 mg	Tablet	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Elbasvir/ grazoprevir (Zepatier)	50 mg/100 mg	Tablet	666.9400	50 mg/100 mg daily	12 weeks[i]	56,023	56,023
Elbasvir/ grazoprevir (Zepatier) plus RBV	50 mg/100 mg	Tablet	666.9400	50 mg/100 mg daily	16 weeks[j]	74,697	77,945 to 80,381
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	800 mg to 1,400 mg daily		3,248 to 5,684	

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Ledipasvir/ sofosbuvir (Harvoni)	90 mg/400 mg	Tablet	797.6190	90 mg/400 mg daily	8 to 24 weeks[k]	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)	44,667 67,000 to 134,000
Ombitasvir/paritaprevir/ ritonavir plus dasabuvir (Holkira Pak)	12.5 mg/75 mg/50 mg 250 mg	Tablet	665.0000[l]	25 mg/150 mg/ 100 mg ombitasvir/ paritaprevir/ ritonavir daily + 250 mg dasabuvir twice daily	12 weeks[m]	55,860	55,860
Ombitasvir/paritaprevir/ ritonavir plus dasabuvir (Holkira Pak) plus RBV	12.5 mg/75 mg/50 mg 250 mg	Tablet	665.0000[l]	25 mg/150 mg/ 100 mg ombitasvir/ paritaprevir/ ritonavir daily + 250 mg dasabuvir twice daily	12 to 24 weeks[m]	55,860 to 111,720	55,860 to 111,720
	200 mg 400 mg 600 mg		0.0001[l]	1,000 mg to 1,200 mg daily			
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tablet	654.7619	400 mg daily	24 weeks[n]	110,000	116,090 to 117,308
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		6,090 to 7,308	
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Caplet	434.5500	150 mg daily	12 to 24 weeks[o]	36,502 to 73,004	91,502 to 183,004
	400 mg	Tablet	654.7619	400 mg daily		55,000 to 110,000	
Direct-acting antivirals in combination with pegylated interferon alpha plus ribavirin therapy							
Daclatasvir plus Asunaprevir plus PR *Genotype 1*	60 mg	Tablet	428.5714	60 mg daily	24 weeks	72,000	94,777
	100 mg	Tablet	38.6905	100 mg twice daily		13,000	
	180 mcg/ 200 mg	Vial/tablet	407.3900	60 mg daily plus 100 mg twice daily + PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day		9,777	
Sofosbuvir (Sovaldi) plus PR	400 mg	Tablet	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg/ 200 mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 1,000 to 1,200 mg daily		4,889	
Simeprevir (Galexos) plus PR	150 mg	Caplet	434.5500	150 mg daily	12 weeks	36,502	46,279 to 56,057
	180 mcg/ 200 mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 800 mg/day to 1,200 mg/day	24 to 48 weeks[p]	9,777 to 19,555	
Boceprevir (Victrelis) plus PR	200 mg	Caplet	12.5000	800 mg three times daily added after 4 weeks PR	24 to 44 weeks	25,200 to 46,200	37,475 to 67,243

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
	120 mcg/ 200 mg	Pens/ caplet	876.7800	PegIFN 1.5 mcg/kg/week; RBV 800 mg/day to 1,400 mg/day[q]	28 to 48 weeks[q]	12,275 to 21,043	

HCV = hepatitis C virus; NA = not available; PegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (September 2017) unless otherwise indicated.[8]
[a] Manufacturer's submitted price.[3]
[b] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.
[c] Delta PA (October 2017).[9]
[d] 8 weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors without cirrhosis.
[e] 12 weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors with cirrhosis, or genotype 1 treatment-experienced patients with NS3/4A inhibitors (NS5A inhibitor naive).
[f] 16 weeks for all treatment-experienced genotype 3 patients and genotype 1 patients with NS5A inhibitor experience (NS3/4A inhibitor naive).
[g] For patients with HCV genotypes 1, 2, or 3 without cirrhosis or liver transplantation.
[h] For patients with HCV genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.
[i] 12 weeks for genotype 1 treatment-naive and treatment-experienced relapsers, as well as for treatment-experienced on-treatment virologic failure in patients with genotype 1b. Eight weeks can be considered in treatment-naive genotype 1b patients without significant fibrosis or cirrhosis.
[j] For genotype 1a patients with treatment-experienced on-treatment virologic failure.
[k] 12 weeks for genotype 1 treatment-naive patients (with or without cirrhosis) and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. Eight weeks can be considered in treatment-naive patients without cirrhosis who have a pre-treatment HCV RNA of less than 6 million IU/mL.
[l] List price is $665 per daily dose. Moderiba brand ribavirin is reimbursed at 0.0001 per tablet when used by Holkira Pak patients. When not provided free of charge, a 12- to 24-week course of ribavirin would cost $3,045 to $7,308 per patient.
[m] 12 weeks of Holkira Pak alone for patients with genotype 1b without cirrhosis; 12 weeks of Holkira Pak plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks of Holkira Pak plus RBV for patients with genotype 1a with cirrhosis who had a previous null response to pegIFN and RBV.
[n] For treatment-naive and treatment-experienced non-cirrhotic patients with genotype 1 who are ineligible to receive an IFN.
[o] 12 weeks for treatment-naive, prior relapse patients or prior non-responders with or without cirrhosis who are not co-infected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.
[p] 24 weeks for treatment-naive or prior relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. 48 weeks for treatment-naive or prior relapse patients with cirrhosis and HIV coinfection. 48 weeks for prior non-responders with or without cirrhosis and with or without HIV coinfection.
[q] Treatment duration is response guided based on viral load.

Table 4: Cost Comparison Table for Drugs Indicated for HCV Genotype 2

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tablet	714.2857[a]	1 tablet daily	12 weeks	60,000	60,000
Interferon-free regimens							
Sofosbuvir/ velpatasvir (Epclusa)	400 mg/100 mg	Tablet	714.2857	400 mg /100 mg daily[b]	12 weeks	60,000	60,000
Sofosbuvir/ velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tablet	714.2857	400 mg /100 mg daily[b]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[b]		3,045 to 3,654	
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	Tablet	714.2856[c]	300 mg/120 mg daily	8 weeks[d]	40,000	40,000
					12 weeks[e]	60,000	60,000
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi)	60 mg	Tablet	428.5714	60 mg daily	12 weeks[f]	36,000	91,000
	400 mg	Tablet	654.7619	400 mg daily		55,000	
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) plus RBV	60 mg	Tablet	428.5714	60 mg daily	12 weeks[g]	36,000	94,045 to 94,654
	400 mg	Tablet	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tablet	654.7619	400 mg daily	24 weeks	110,000	116,090 to 117,308
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 to 1,200 mg daily		6,090 to 7,308	

HCV = hepatitis C virus; mg = milligrams; RBV = ribavirin.

All prices are from the Saskatchewan Drug Plan online formulary (July 2017) unless otherwise indicated.[8]

[a] Manufacturer's submitted price.[3]

[b] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.

[c] Delta PA (October 2017).[9]

[d] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors without cirrhosis.

[e] 12 weeks for all treatment-naive patients with cirrhosis, genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors with cirrhosis, or genotype 1 treatment-experienced patients with NS3/4A inhibitors (NS5A inhibitor naive).

[f] For patients with HCV genotypes 1, 2, or 3 without cirrhosis or liver transplantation.

[g] For patients with HCV genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.

Table 5: Cost Comparison Table for Drugs Indicated for HCV Genotype 3

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	400 mg/ 100 mg/100 mg	Tablet	714.2857[a]	1 tablet daily	12 weeks	60,000	60,000
Interferon-free regimens							
Sofosbuvir/ velpatasvir (Epclusa)	400 mg/100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	60,000
Sofosbuvir/ velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[b]		3,045 to 3,654	
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	Tablet	714.2856[c]	300 mg/120 mg daily	8 weeks[d]	40,000	40,000
					12 weeks[e]	60,000	60,000
					16 weeks[f]	80,000	80,000
Elbasvir/ grazoprevir (Zepatier) plus Sofosbuvir (Sovaldi)	100 mg/50 mg	Tablet	666.9400	50 mg/100 mg daily	12 weeks	56,023	111,023
	400 mg		654.7619	400 mg daily		55,000	
Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi)	60 mg	Tablet	428.5714	60 mg daily	12 weeks[g]	36,000	91,000
	400 mg	Tablet	654.7619	400 mg daily		55,000	
Daclatasvir (Daklinza) plus Sofosbuvir (Sovaldi) plus RBV	60 mg	Tablet	428.5714	60 mg daily	12 weeks[h]	36,000	94,045 to 94,654
	400 mg	Tablet	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tablet	654.7619	400 mg daily	24 weeks	55,000	58,045 to 58,654
	200 mg 400 mg 600 mg	Tablet	7.2500 14.5000 21.7500	1,000 to 1,200 mg daily		3,045 to 3,654	

HCV = hepatitis C virus; mg = milligrams; RBV = ribavirin.

All prices are from the Saskatchewan Drug Plan online formulary (July 2017) unless otherwise indicated.[8]

[a] Manufacturer's submitted price.[3]

[b] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.

[c] Delta PA (October 2017).[9]

[d] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors without cirrhosis.

[e] 12 weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors with cirrhosis, or genotype 1 treatment-experienced patients with NS3/4A inhibitors (NS5A inhibitor naive).

[f] 16 weeks for all treatment-experienced genotype 3 patients and genotype 1 patients with NS5A inhibitor experience (NS3/4A inhibitor naive).

[g] For patients with HCV Genotypes 1, 2, or 3 with compensated or decompensated cirrhosis or who are post-liver transplantation.

[h] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.

Table 6: Cost Comparison Table for Drugs Indicated for HCV Genotype 4

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	400 mg/ 100 mg/100 mg	Tablet	714.2857[a]	1 tablet daily	12 weeks	60,000	60,000
Interferon-free regimens							
Sofosbuvir/ velpatasvir (Epclusa)	400 mg/100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	60,000
Sofosbuvir/ velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[b]		3,045 to 3,654	
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	Tablet	714.2856[c]	300 mg/120 mg daily	8 weeks[d]	40,000	40,000
					12 weeks[e]	60,000	60,000
Elbasvir/ grazoprevir (Zepatier)	50 mg/100 mg	Tablet	666.9400	50 mg/100 mg daily	12 weeks[f]	56,023	60,300
Elbasvir/ grazoprevir (Zepatier) plus RBV	100 mg/50 mg	Tablet	666.9400	50 mg/100 mg daily	16 weeks[g]	74,697	77,945 to 80,381
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	800 mg to 1,400 mg daily		3,248 to 5,684	
Ombitasvir/paritaprevir/ritonavir (Technivie) plus RBV	12.5 mg 75 mg 50 mg	Tablet	665.0000 per two tabs	25 mg/150 mg/ 100 mg daily	12 weeks[f]	55,860	58,905 to 59,514
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Caplet	434.5500	150 mg daily	12 to 24[h] weeks	36,502 to 73,004	91,502 to 183,004
	400 mg	Tablet	654.7619	400 mg daily		55,000 to 110,000	
Direct-acting antivirals in combination with peginterferon alpha plus ribavirin therapy							
Daclatasvir (Daklinza) plus asunaprevir (Sunvepra) plus PR	60 mg	Tablet	428.5714	60 mg daily	24 weeks	72,000	NA
	100 mg	Tablet	NA	100 mg twice daily		NA	
	180 mcg /200mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day		9,777	
Sovaldi (sofosbuvir) plus PR	400 mg	Tablet	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg /200mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day		4,889	

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Simeprevir (Galexos) plus PR	150 mg	Caplet	434.5500	150 mg daily	12 weeks	36,502	56,057
	180 mcg /200mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day	48 weeks[h]	19,555	

HCV = hepatitis C virus; mcg = micrograms; mg = milligrams; NA = not available; PegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (July 20) unless otherwise indicated.[8]

[a] Manufacturer's submitted price.[3]

[b] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.

[c] Delta PA (October 2017).[9]

[d] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors without cirrhosis.

[e] 12 weeks for all treatment-naive patients with cirrhosis, genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors with cirrhosis, or genotype 1 treatment-experienced patients with NS3/4A inhibitors (NS5A inhibitor naive).

[f] 12 weeks for genotype 4 treatment-naive and treatment-experienced relapsers.

[g] For genotype 4 patients with treatment-experienced on-treatment virologic failure.

[h] 12 weeks for treatment-naive, prior relapse patients or prior non-responders with or without cirrhosis who are not co-infected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.

[i] 48 weeks for genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV coinfection.

Table 7: Cost Comparison Table for Drugs Indicated for HCV Genotypes 5 and 6

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for 1 Course of Therapy ($)	Total Cost for 1 Course of Combo Therapy ($)
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	400 mg/ 100 mg/100 mg	Tablet	714.2857[a]	1 tablet daily	12 weeks	60,000	60,000
Interferon-free regimens							
Sofosbuvir/ velpatasvir (Epclusa)	400 mg/ 100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	60,000
Sofosbuvir/ velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tablet	714.2857	400 mg/100 mg daily[b]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg		7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[b]		3,045 to 3,654	
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	Tablet	714.2856[c]	300 mg/120 mg daily	8 weeks[d]	40,000	40,000
					12 weeks[e]	60,000	60,000
Direct-acting antivirals in combination with peginterferon alpha plus ribavirin therapy							
Sovaldi (sofosbuvir) plus PR	400 mg	Tablet	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg /200mg	Vial/tablet	407.3900	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day		4,889	

HCV = hepatitis C virus; mcg = micrograms; mg = milligrams; PegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (July 20) unless otherwise indicated.[8]
[a] Manufacturer's submitted price.[3]
[b] 12 weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.
[c] Delta PA (October 2017).[9]
[d] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors without cirrhosis.
[e] 12 weeks for all treatment-naive patients with cirrhosis, genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A and NS3/4A inhibitors with cirrhosis, or genotype 1 treatment-experienced patients with NS3/4A inhibitors (NS5A inhibitor naive).

Appendix 2: Additional Information

Table 8: 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 9: Author information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

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

Appendix 3: Reviewer Worksheets

Manufacturer's Model Structure

A Markov state transition model was developed to describe the progression of disease over a lifetime horizon (80 years). The model consisted of nine states, with transitional probabilities describing the movement between the states. Costs, utility, mortality, and morbidity were associated with each state. The model structure is shown in Figure 1.

The model maintained different cirrhosis states (non-cirrhotic [NC]: METAVIR fibrosis scores F0-F3, and cirrhotic [CC]: METAVIR score F4). The manufacturer noted that CC patients have worse outcomes in the nearer term and had lower sustained virologic response (SVR) rates with previous treatments. The manufacturer's model also permitted use of a blended NC/CC population. Results for a blended population depended on the proportion of CC to NC patients. In the default, the proportion was set at that observed in the POLARIS trials. However, no results were presented in the manufacturer's report for a blended CC/NC population.

The manufacturer's model maintained different treatment experience states (i.e., NS5A naive and NS5A experienced). These populations had different comparators and different SVR outcomes. Results were produced in the NS5A-naive and NS5A-experienced populations, each of which was sub-divided by cirrhosis status.

Patients entered the model and underwent treatment. They moved to the SVR health state after completing treatment if they had undetectable hepatitis C virus ribonucleic acid (HCV RNA) 12 weeks after the end of treatment. Patients who achieved SVR were considered to have permanently cleared the virus, with no spontaneous reactivation of the HCV infection or re-infection in the base case. NC patients had no risk of future hepatic sequelae from HCV. Cirrhotic patients with SVR continued to have cirrhosis, but with a reduced risk of progression to more severe health states. Patients without a SVR faced an annual probability of progressing from F0 through to F4, decompensated cirrhosis (DCC), and other outcomes as if they had not received antiviral treatment.

Patients in both compensated and decompensated cirrhosis stages could progress to HCC. Patients with DCC or HCC could progress to liver transplant. Following liver transplantation, patients had a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase, patients remained at a higher risk of death as compared with the general population.

Age- and gender-specific general population mortality rates were applied to each health state in the model. Additionally, excess hepatic mortality was assigned to patients in the last and most severe states: DCC, HCC, liver transplant, and post-liver transplantation.

In the CADTH Therapeutic Review,[6] patients entered the model with a mean age of 50 years with a predetermined distribution of patients across fibrosis scores. The manufacturer used a mean age of 58 years based on mean age at randomization in the POLARIS trials. As a result, the distribution of fibrosis scores was skewed to more advanced disease for the older patient population. The manufacturer assumed that patients with more advanced disease were to be prioritized for treatment upon initial access to the highly effective DAA therapies. The distribution of fibrosis scores, as observed in the POLARIS trials, was used in the economic model and was assumed by the manufacturer to reflect clinical practice in Canada.[3]

Table 10: Fibrosis Distribution Based on POLARIS Trials

Setting	F0	F1	F2	F3	F4
NS5A naive	6.0%	5.5%	22.5%	18.1%	46.7%
NS5A experienced	5.3%	4.6%	20.2%	22.8%	46.0%

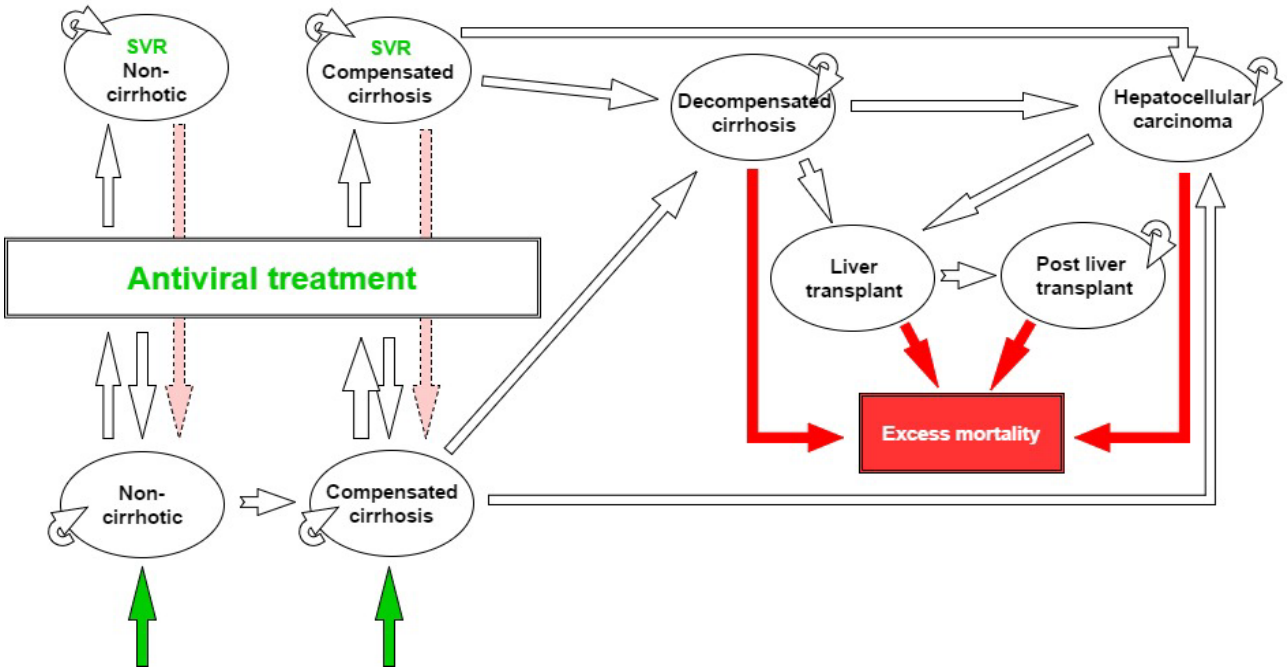
Source: Manufacturer's pharmacoeconomic submission.[3]

The manufacturer's model permitted the percentage of patients in the F3 state to be varied for NC patients because these patients transition to CC and are at higher risk for DCC, HCC, liver transplant, and death.

The percentage of patients in the F4 state (CC) was assumed to be 100% for the CC population and 0% for the NC population, and could be varied for a blended NC/CC population. As a default, the distribution observed in POLARIS was used by the manufacturer in the model (46% CC).[3]

Background mortality occurs in each health state. The red arrows and health state "excess mortality" represent the disease-specific mortality associated with having DCC, liver transplant, or HCC. Dashed pink arrows represent health-state transitions only investigated in a sensitivity analysis. Green arrows represent the model entry points.

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's pharmacoeconomic submission.[3]

The effectiveness data for SOF/VEL/VOX are taken as SVR rates 12 weeks after the end of treatment within the active arms of two phase III trials: POLARIS-1 and POLARIS-4.[4] For patient with no cirrhosis or CC, these trials compared 12 weeks of SOF/VEL/VOX to either placebo (POLARIS-1) or 12 weeks of SOF/VEL (POLARIS-4).

Table 11: Model Comparators

Trial Name	Interventions	Population	Sample Size
POLARIS-1[4]	SOF/VEL/VOX x 12 weeks No treatment (placebo)	GT1 to 6 NS5A experienced	414 (46% CC)
POLARIS-4 [4]	SOF/VEL/VOX x 12 weeks SOF/VEL x 12 weeks	GT1 to 4 SOF experienced NS5A naive	333 (46% CC)

Source: Manufacturer's pharmacoeconomic submission.[3]
CC = compensated cirrhosis; GT = genotype; NC = non-cirrhotic; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

The breakdown by comparator for POLARIS-1 and -4 was as follows:

- POLARIS-1, GT1: SOF/VEL/VOX (n = 150), placebo (n = 150)
- POLARIS-1, GT2-6: SOF/VEL/VOX (n = 114)
- POLARIS-4, GT1, 2, or 3: SOF/VEL/VOX (n = 163), SOF/VEL (n = 151)
- POLARIS-4, GT4: SOF/VEL/VOX (n = 19).

Previous treatment history varied for the NS5A-experienced patients, but it most commonly involved an NS5A inhibitor plus NS5B inhibitor (SOF) such as SOF/ledipasvir or SOF + daclatasvir (78%). For the NS5A-naive patients, previous treatment was most commonly SOF alone (74%).

In POLARIS-1, patients with genotype 1 HCV infection were randomized 1:1 to 12 weeks of SOF/VEL/VOX or an identical-looking placebo, stratified by the presence or absence of cirrhosis. Patients with other genotypes were assigned to receive 12 weeks of SOF/VEL/VOX.[4] In POLARIS-4, patients with HCV genotype 1, 2, or 3 were randomized at a 1:1 ratio to 12 weeks of SOF/VEL/VOX or SOF/VEL, stratified by the presence or absence of cirrhosis and HCV genotype (1, 2, or 3) and cirrhosis status. Patients with other genotypes were assigned to receive 12 weeks of SOF/VEL/VOX.[3]

Table 12: Sustained Virologic Response Rates, POLARIS-1 and POLARIS-4

Trial Name	Interventions	Population	Sample Size
	SOF/VEL/VOX N = 263 (%)	SOF/VEL/VOX N =182 (%)	SOF/VEL N =151 (%)
By NS5A experience, genotype, and cirrhosis state combined			
GT3 – NC	22/22 (100)	22/23 (96)	21/22 (96)
GT3 – CC	52/56 (93)	29/31 (94)	23/30 (77)
Non-GT3 – NC	118/120 (98)	74/75 (99)	56/60 (93)
Non-GT3 – CC	61/65 (94)	52/53 (98)	36/39 (92)
By previous treatment			
NS5A + NS5B	151/161 (94)	NA	NA
NS5A + NS3 +/- NS5B	83/83 (100)	NA	NA
NS5A +/– Others	18/18 (100)	NA	NA
Others	1/1 (100)	NA	NA
NS5B only	NA	130/134 (97)	99/109 (91)
NS5B +/– NS3	NA	45/46 (98)	33/38 (87)
Others	NA	2/2 (100)	3/3 (100)

Source: Manufacturer's pharmacoeconomic submission.[3]
CC = compensated cirrhosis; GT = genotype; NA = not applicable; NC = non-cirrhotic; NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; NS5B = nonstructural protein 5B; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

The comparators were no treatment (both populations) and SOF/VEL (NS5A-naive patients only). In a model the manufacturer had submitted previously, HCV therapies were specific to genotype, because comparator regimens/dosages or SVR rates differed by genotype. The manufacturer had anticipated that SOF/VEL could be effective in patients who have previously been exposed to an NS5B inhibitor (typically SOF); therefore, SOF/VEL was selected as a comparator for POLARIS-4 (i.e., for patients who had not previously received an NS5A inhibitor). However, SOF/VEL does not have a specific indication for this population, and clinical experience is limited. As there are no other approved DAA regimens in Canada for previous NS5B inhibitor treatment failure, no treatment was also included as a comparator for NS5A-naive patients.

For patients who have previously failed an NS5A inhibitor, no treatment was determined by the manufacturer to be the only appropriate comparator based on the POLARIS-1 trial and the fact that no DAA regimens are approved or recommended in Canada specifically for re-treatment of NS5A inhibitor failures.[3] Furthermore, consequent to their low prevalence, the numbers of POLARIS patients with GT4, 5, or 6 were too low to support genotype-specific analyses by the manufacturer. Therefore, the manufacturer included all genotypes in the model, and the genotypes were considered together in the base case. In a non-base-case analysis, GT3 versus non-GT3 patients were examined separately.

The natural history transition rates (including CHC-related mortality) are based upon a number of different trials, but the annual probabilities correspond with those used in the CADTH Therapeutic Review.[6] As the manufacturer's model includes potential treatment for those in DCC, the model allows for a DCC-SVR transition, with the transition probabilities based on data from van der Meer et al.[10]

Utility data were taken from multiple sources, including an increment for SVR (0.07) from the recent CADTH Therapeutic Review.[6] Utility data were taken from a variety of trials but were

broadly consistent with the CADTH Therapeutic Review.[6] In contrast with the review, however, the manufacturer did not assign a disutility to adverse events. Costs were broken down into treatment costs, drug management costs, adverse event costs, and health-state costs.

The drug treatment cost for SOF/VEL was obtained from the Ontario provincial formulary.[3] Drug management costs were assigned for diagnostic work-up and preparation for initiation of drug therapy at a baseline visit as well as for each visit and a final assessment at week 12 post-treatment to assess SVR these costs were obtained from public sources. Adverse event costs were limited to the cost attributed to diarrhea in patients on SOF/VEL/VOX based on clinician opinion. The cost for each health state was determined from the literature in alignment with the CADTH Therapeutic Review.[6] The primary source was a large Canadian costing study using administrative data[11] plus a separate Canadian costing study for liver transplant-related costs.[12]

The time horizon was assumed to be lifetime (80 years of age) with a model cycle length of one year. A discount rate of 1.5% was applied to both costs and consequences on an annual basis. [3]

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	The effectiveness estimate (SVR rates) was taken from the active intervention arms of pivotal trials.[4]	There is a high potential for bias in the estimates produced by observed SVR rates in the clinical trials.
Natural history	The natural history transition rates (including CHC-related mortality) are drawn from a number of different trials.	The annual probabilities correspond with those used in the CADTH Therapeutic Review.[6]
Utilities	Utilities are taken from a variety of sources, including the CADTH Therapeutic Review.[6]	Where applied, the utilities used appear to correspond to the CADTH Therapeutic Review in all cases. However, the utilities for AEs were not considered.
Resource use	The manufacturer considers costs for health states, drug acquisition, and AEs. The manufacturer uses clinical judgment to formulate scenarios for monitoring costs, using provincial formulary unit costs to obtain cost figures.	
AEs (indicate which specific AEs were considered in the model)	The model considers four AEs: headache, fatigue, diarrhea and nausea.	This approach is consistent with several prior CADTH reviews.
Mortality	Age and gender-specific mortality rates were taken from Statistics Canada. Annual background mortality was applied to patients in all health states.[3] Excess mortality data were applied to the decompensated cirrhotic, transplant, and hepatocellular cancer states.	The CADTH Therapeutic Review made similar assumptions.
Costs		
Drug	From provincial formularies, as per the CADTH Therapeutic Review[13]	
AEs	Based on clinician opinion	Validated by CDR clinical expert
Health state	Based on CADTH Therapeutic Review	The authors state an extra source for costs

Data Input	Description of Data Source	Comment
	Based on expert opinion for F0-F3 and SVR F0-F3	following liver transplantation; the same source was used by the CADTH Therapeutic review
Monitoring	The manufacturer states that data were obtained by clinical opinion.	Validated by CDR clinical expert

AE = adverse event; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; SVR = sustained virologic response.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
The manufacturer uses POLARIS-1 and POLARIS-4 to provide multiple scenarios covering a large population of cirrhotic and/or treatment-experienced patients.	Both trials share the same limitations related to comparisons with a performance goal of 85%, rather than a direct comparison between trial groups, which limits the ability to assess differences between the randomized treatments. The trials represent a chronic HCV population with few comorbidities (i.e., milder liver fibrosis, lower baseline HCV RNA levels, minimal kidney function impairment, etc.). Most patients included had a fibrosis stage of F0-F1, with less than 20% having advanced fibrosis or cirrhosis (F3 or F4).
The manufacturer's model included a DCC health state with assigned health-state costs and utility value.	Although the DCC health state included excess hepatic mortality, it did not include information on the expected effects and costs of SOF/VEL/VOX in patients with DCC, since SOF/VEL/VOX is not indicated for use in patients with DCC.
The hepatocellular carcinoma health state is assigned a distinct, much higher cost than DCC.	Hepatocellular carcinoma health state costs are classified as "late stage" costs within the categories of the CADTH Therapeutic Review (i.e., the same cost is applied to the DCC and HCC states).[6] Using the approach of the CADTH review, the costs per year are around one-third of the cost applied by the manufacturer.

DCC = decompensated cirrhosis; HCV = hepatitis C virus; RNA = ribonucleic acid; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir.

Manufacturer's Results

Total costs were higher for the CC population versus the NC population, while total QALYs were lower in the manufacturer's base-case analysis. There was little difference in either total costs or total QALYs for the NS5A-naive versus NS5A-experienced populations. SOF/VEL/VOX dominated SOF/VEL for NS5A-naive patients, with higher QALY gains and lower overall costs. SOF/VEL/VOX had the same drug cost as SOF/VEL but lower overall costs due to its higher SVR rates. The incremental cost-utility ratios for SOF/VEL/VOX versus no treatment for all patients were near $6,000/QALY for NC patients and $12,000/QALY for CC patients (Table 2). The sequential analysis is shown in Table 15 below.

Table 15: Results of Manufacturer Base Case Sequential Analysis for SOF/VEL/VOX by Cirrhosis Status

Treatment	Total Costs ($)	Total QALYs	ICUR vs. No Treatment ($/QALY)	Sequential ICUR ($/QALY)
NC				
No treatment	$49,462	11.73		
SOF/VEL /VOX	$63,561	13.98	$6,254	$6,254
SOF/VEL	$65,521	13.89	$7,431	Dominated by SOF/VEL/VOX
CC				
No treatment	$105,406	8.74		
SOF/VEL /VOX	$150,471	12.61	$11,638	$11,638
SOF/VEL	$152,359	12.17	$13,675	Dominated by SOF/VEL/VOX

Source: manufacturer's pharmacoeconomic submission.[3]
CC = compensated cirrhosis; ICUR = incremental cost-utility ratio; NC = non-cirrhotic; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

Table 16: Results of Manufacturer Scenario Analysis for SOF/VEL/VOX (GT3)

Population/Comparator	Total Costs ($)	Total QALYs	ICUR
NS5A experienced			
Non-cirrhotic patients			
No treatment	$55,606	11.51	
SOF/VEL/VOX	$62,568	14.03	$2,760
Compensated cirrhosis patients			
No treatment	$105,406	8.74	
SOF/VEL/VOX	$151,093	12.47	$12,253
NS5A naive			
Non-cirrhotic patients			
Comparator: No treatment			
No treatment	$55,606	11.51	
SOF/VEL/VOX	$64,951	13.92	$3,874
Comparator: SOF/VEL			
SOF/VEL	$65,044	13.92	SOF/VEL/VOX dominates
SOF/VEL/VOX	$63,951	13.92	
Compensated cirrhosis patients			
Comparator: No treatment			
No treatment	$105,406	8.74	
SOF/VEL/VOX	$150,973	12.49	$12,130
Comparator: SOF/VEL			
SOF/VEL	$153,898	11.81	SOF/VEL/VOX dominates
SOF/VEL/VOX	$150,973	12.49	

Source: Manufacturer's pharmacoeconomic submission[3]
GT3 = genotype 3; ICUR = incremental cost-utility ratio; NS5A = nonstructural viral protein 5A; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

Table 17: Results of Manufacturer Scenario Analysis for SOF/VEL/VOX (Non-GT3)

Population/Comparator	Total Costs ($)	Total QALYs	ICUR
NS5A experienced			
Non-cirrhotic patients			
No treatment	$46,370	11.84	
SOF/VEL/VOX	$63,327	14.00	$7,861
Compensated cirrhosis patients			
No treatment	$105,406	8.74	
SOF/VEL/VOX	$150,921	12.50	$12,078
NS5A naive			
Non-cirrhotic patients			
Comparator: No treatment			
No treatment	$46,370	11.84	
SOF/VEL/VOX	$63,175	14.00	$7,764
Comparator: SOF/VEL			
SOF/VEL	$65,592	13.89	SOF/VEL/VOX dominates
SOF/VEL/VOX	$63,175	14.00	
Compensated cirrhosis patients			
Comparator: No treatment			
No treatment	$105,406	8.74	
SOF/VEL/VOX	$150,178	12.68	$11,364
Comparator: SOF/VEL			
SOF/VEL	$151,174	12.44	SOF/VEL/VOX dominates
SOF/VEL/VOX	$150,178	12.68	

Source: Manufacturer's pharmacoeconomic submission.[3]
GT3 = genotype 3; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

CADTH Common Drug Review Reanalyses

In the manufacturer's base-case analysis, the annual costs associated with cirrhotic health states (DCC, HCC, and liver transplant) were derived from the CADTH Therapeutic Review from the patient age range of 45 to 54. The manufacturer's model uses an entry patient age of 58; therefore, CDR utilized the annual costs from the CADTH Therapeutic Review for the age range of 55 to 64. The manufacturer's model also classified HCC health-state costs as pre-death stage costs, while the CADTH Therapeutic Review classified them as "late stage" costs (i.e., the same cost is applied to the DCC and HCC states). Using the approach of the CADTH review, the costs per year for HCC were modified to be similar to those of DCC. The results of the CDR reanalysis did not significantly impact the manufacturer's base case results for NC patients, but in the cirrhotic group, SOF/VEL/VOX was not dominant over SOF/VEL and had resulted in an incremental cost-utility ratio of $923 per QALY (Table 18).

Table 18: Results of CDR Reanalysis for SOF/VEL/VOX

Population/Comparator	Total Costs ($)		Total QALYs		ICUR
	SOF/VEL/VOX	Comparator	SOF/VEL/VOX	Comparator	
NS5A Experienced NC					
No treatment	$63,206	$46,143	13.99	11.73	$7,520
NS5A Naive NC					
SOF/VEL	$63,493	$65,319	13.98	13.89	SOF/VEL/VOX dominates
No treatment	$63,493	$46,143	13.98	11.73	$7,696
NS5A Experienced CC					
No treatment	$160,826	$95,634	12.49	8.74	$17,384
NS5A Naive CC					
SOF/VEL	$160,935	$160,530	12.61	12.17	$923
No treatment	$160,935	$95,634	12.61	8.74	$16,864

CC = compensated cirrhosis; ICUR = incremental cost-utility ratio; NC = non-cirrhotic; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

Table 19: Results of CDR Sequential Reanalysis for SOF/VEL/VOX by Cirrhosis Status

Treatment	Total Costs ($)	Total QALYs	ICUR vs. No Treatment ($/QALY)	Sequential ICUR ($/QALY)
NC				
No treatment	$46,143	11.73		
SOF/VEL	$65,319	13.89	$8,874	Extended dominance by no treatment and SOF/VEL/VOX
SOF/VEL/VOX	$63,493	13.98	$7,696	$7,696
CC				
No treatment	$95,634	8.74		
SOF/VEL	$160,530	12.17	$18,901	Extended dominance by no treatment and SOF/VEL/VOX
SOF/VEL/VOX	$160,935	12.61	$16,864	$16,864

CC = compensated cirrhosis; ICUR = incremental cost-utility ratio; NC = non-cirrhotic; QALY = quality-adjusted life-year; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir.

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