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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

GLECAPREVIR / PIBRENTASVIR (MAVIRET)

(AbbVie Corporation)

Indication: Hepatitis C genotype 1 to 6

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Abbreviations

DAA	direct-acting antiviral
DCC	decompensated cirrhosis
DSV	dasabuvir
GP	glecaprevir/pibrentasvir
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
NS3/4A	nonstructural viral protein 3/4A
NS5A	nonstructural viral protein 5A
OBV/PTV/r	ombitasvir/paritaprevir/ritonavir
PRS	pegylated interferon plus ribavirin plus sofosbuvir
QALY	quality-adjusted life-year
SVR	sustained virological response

Table 1: Summary of the Manufacturer's Economic Submission

<table>
<tr><td>Drug Product</td><td>GP (Maviret)</td></tr>
<tr><td>Study Question</td><td>To assess the cost-effectiveness of GP versus other available therapies in the treatment of adult patients with HCV genotypes 1 to 6 in Canada</td></tr>
<tr><td>Type of Economic Evaluation</td><td>Cost-utility analysis</td></tr>
<tr><td>Target Population</td><td>Adult patients with chronic HCV infection (genotypes 1 to 6): treatment-naive and treatment-experienced, with or without compensated cirrhosis</td></tr>
<tr><td>Treatment</td><td>Treatment-naive patients, genotype 1 to 6:
• without cirrhosis: 8 weeks
• with cirrhosis: 12 weeks

Treatment-experienced patients on PRS:
• genotype 1, 2, 4, 5, 6, without cirrhosis: 8 weeks
• genotype 1, 2, 4, 5, 6, with cirrhosis: 12 weeks
• genotype 3, with or without cirrhosis: 16 weeks

• Treatment-experienced patients on NS3/4A protease inhibitor (NS5A inhibitor-naive), genotype 1 with or without cirrhosis: 12 weeks

• Treatment-experienced patients on NS5A inhibitor (NS3/4A protease inhibitor-naive), genotype 1 with or without cirrhosis: 16 weeks</td></tr>
<tr><td>Outcome</td><td>QALYs</td></tr>
<tr><td>Comparator(s)</td><td>Portfolio analysis (pan-genotypic overall HCV population)
• genotype 1: SOF/LDV (12 weeks)
• genotype 2: SOF + RBV (12 weeks)
• genotype 3 to 6: SOF/VEL (12 weeks)

Segment analysis: Comparison of one intervention versus one comparator within a pre-specified patient segment according to genotype, treatment history, and presence/absence of cirrhosis

<table>
<tr><th>Comparator</th><th>Genotype 1</th><th>Genotype 2</th><th>Genotype 3</th><th>Genotype 4</th><th>Genotype 5</th><th>Genotype 6</th></tr>
<tr><td>SOF/LDV (12 weeks)</td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>OBV/PTV/r/DSV (12 weeks)</td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>EBR/GZR (12 weeks)</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>SOF/VEL (12 weeks)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>No treatment</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
</td></tr>
<tr><td>Perspective</td><td>Canadian publicly funded health care system</td></tr>
<tr><td>Time Horizon</td><td>Lifetime (70 years in the base case)</td></tr>
</table>

Results for Base Case	Portfolio analysis: GP dominates all comparators.
	
	Segment analysis:
	• Genotype 1:
	  • treatment-naive patients without cirrhosis: GP dominated the comparators except “no treatment” (ICUR of $2,319 per QALY)
	  • treatment-naive patients with cirrhosis: GP dominated SOF/VEL (lower cost, greater QALYs for GP)
	  • PRS-experienced: ICUR for GP versus SOF/VEL ranged from being dominated (with cirrhosis) — GP higher costs and fewer QALYs — to being dominant (without cirrhosis)
	  • NS3/4A treatment experience: ICUR for GP versus no treatment was $6,383 per QALY, and GP dominated EBR/GZR
	  • NS5A treatment experience, the ICUR for GP versus no treatment was $13,097 per QALY.
	• Genotype 3:
	  • treatment-naive patients without cirrhosis: ICUR for GP versus no treatment was $1,380 per QALY
	  • treatment-naive patients with cirrhosis: GP dominated SOF/VEL
	  • PRS treatment experience: ICUR for GP versus SOF/VEL was $99,877 per QALY versus SOF/VEL (without cirrhosis) and $69,314 per QALY versus SOF/VEL (with cirrhosis)
	• Genotype 2, 4, 5, and 6:
	  • treatment-naive patients without cirrhosis: ICUR for GP ranges from $2,582 to $5,891 per QALY versus no treatment
	  • treatment-naive patients with cirrhosis: GP was dominated (greater costs, few QALYs) by SOF/VEL
	  • PRS-experienced patients without cirrhosis: ICUR for GP ranges from $1,713 to $5,919 per QALY versus no treatment
	  • PRS-experienced patients with cirrhosis: GP was dominated by SOF/VEL.

Key Limitations	CDR identified a number of major limitations with the submitted analyses: • The portfolio approach submitted by the manufacturer was considered invalid based on the approved indications for GP in genotypes based on treatment experience and presence or absence of cirrhosis. • There was uncertainty with the clinical evidence for GP for two reasons: effectiveness parameters are drawn from non-comparative trials, and the sample size of many subgroups with reported SVR rates of 100% is low and the uncertainty in these estimates is not accounted for appropriately. • The efficacy parameters in segment analysis in genotype 1 patients previously treated with an NS3/4A protease inhibitor or NS5A inhibitors were based on a clinical trial that was not designed or powered to test for subgroup effects. • The efficacy for EBR/GZR in the same analysis was based on a study that used an unapproved dosage for EBR/GZR. • The manufacturer did not include a disutility value for adverse events, including anemia, depression, and rash.
CDR Estimate(s)	• The limitations specific to the portfolio approach included clinical information, and disutility with adverse events could not be addressed by CDR. As a result, the interpretation of the presented analyses warrants cautious consideration. • A price reduction of 3% for GP is required to ensure GP is cost-effective across all subgroups of genotype 1 and genotype 2 (ICUR is < $50,000 per QALY in all cases). • In genotype 3 patients experienced with PRS, a 12% price reduction would be necessary for GP to achieve an ICUR of $48,627 per QALY compared with SOF/VEL in patients without cirrhosis, and a 7% reduction to achieve an ICUR of $48,228 per QALY compared with SOF/VEL in patients with cirrhosis. • No conclusions could be drawn regarding the cost-effectiveness of GP for patients with genotype 4, 5, or 6, due to the limited data included in the submitted model.

CDR = CADTH Common Drug Review; EBR/GZR = elbasvir/grazoprevir; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; ICUR = incremental cost-utility ratio; NS = nonstructural protein; OBV/PTV/r/DSV = ombitasvir/paritaprevir/ritonavir/dasabuvir; PRS = pegylated interferon plus ribavirin plus sofosbuvir; QALY = quality-adjusted life-year; SOF + RBV = sofosbuvir and ribavirin; SOF/LDV = sofosbuvir/ledipasvir; SOF/VEL = sofosbuvir/velpatasvir; SVR = sustained virologic response.

Drug	Glecaprevir/pibrentasvir (Maviret)
Indication	For the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with an NS3/4A protease inhibitor but not both classes of inhibitors.
Reimbursement Request	As per indication
Dosage Form(s)	Glecaprevir (100 mg) / pibrentasvir (40 mg) tablet
NOC Date	August 16, 2017
Manufacturer	AbbVie Corporation

Executive Summary

Background

Glecaprevir/pibrentasvir (GP) is a fixed-dose combination of two pan-genotypic direct-acting antiviral (DAA) drugs: glecaprevir, a nonstructural viral protein 3/4A (NS3/4A) protease inhibitor; and pibrentasvir, a nonstructural viral protein 5A (NS5A) inhibitor.[1] GP is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis (Table 2). The recommended dose is three tablets (glecaprevir 300 mg / pibrentasvir 120 mg) once daily for 8 to 16 weeks, depending on the patient's prior treatment experience, genotype and whether cirrhosis is present.[1] At the time of submission, the manufacturer submitted a price of $797.62 for three tablets. This price was reduced by the manufacturer during the review to $714.29 for three tablets, reflecting an approximate 10% reduction in the original price, and corresponding to $40,000 for an 8-week (56-day) treatment, $60,000 for a 12-week (84-day) treatment and $80,000 for a 16-week (112-day) treatment.[2]

Table 2: Indications for Glecaprevir/Pibrentasvir Treatment

HCV Genotype	Treatment History	Cirrhosis Status	Treatment Duration	Total Cost for One Course of Treatment ($)
Genotype 1, 2, 3, 4, 5, 6	Naive	No	8 weeks	40,000
		Yes	12 weeks	60,000
Genotype 1, 2, 4, 5, 6	PRS[a]	No	8 weeks	40,000
		Yes	12 weeks	60,000
Genotype 1	NS3/4A PI[b] (NS5A inhibitor-naive)	Yes/no	12 weeks	60,000
Genotype 1	NS5A[c] (NS3/4A inhibitor-naive)	Yes/no	16 weeks	80,000
Genotype 3	PRS[a]	Yes/no	16 weeks	80,000

BOC = boceprevir; DCV = daclatasvir; HCV = hepatitis C virus; LDV = ledipasvir; NS = nonstructural protein; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; PRS = pegylated interferon/ribavirin plus sofosbuvir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; TPV = telaprevir.
Source: manufacturer's pharmacoeconomic submission.[3]
[a] Experienced with regimens containing PR, SOF + PR, SOF + RBV), but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.
[b] Experienced with regimens containing SMV + SOF or SMV + PR or BOC + PR or TPV + PR.
[c] Experienced with regimens containing DCV + SOF, DCV + PR, or LDV + SOF.

The manufacturer's pharmacoeconomic submission is based on a Markov cohort model, where patients are in health states representing initial METAVIR (fibrosis stage) scores with active chronic HCV infection, sustained virological response, and absorbing mortality states. The manufacturer presents results as both a portfolio approach where the overall HCV patient population is presented (all genotypes, treatment-naive and treatment-experienced, with or without compensated cirrhosis), and as a segmented approach focusing on each patient segment (according to genotype, treatment history, and the presence or absence of cirrhosis). The comparators varied within the 24 subgroups considered and included DAAs with and without ribavirin, and no treatment.

The manufacturer's base-case analysis using a portfolio approach provided an incremental cost-utility ratio (ICUR) that combined all genotypes, regardless of treatment history and presence of cirrhosis, based on the aggregation of subgroup analyses that calculated the outcomes for each segment (i.e., running the model for each fibrosis stage, genotype, and prior treatment history combination against one previously specified comparator). The result of the portfolio approach found GP to dominate the comparators (higher quality-adjusted life-years [QALYs] and lower costs). In the segmented approach, GP appeared to be cost-effective, based on the manufacturer's results for treatment-naive patients without cirrhosis in all subgroups when compared with no treatment. For treatment-naive patients with cirrhosis, the manufacturer's results of GP versus sofosbuvir/velpatasvir ranged from being dominated by sofosbuvir/velpatasvir (genotype 2, 4, 5, and 6), to dominating sofosbuvir/velpatasvir in genotype 1 and 3. In pegylated interferon plus ribavirin plus sofosbuvir (PRS) treatment-experienced patients, the ICUR for GP in genotype 1 compared with sofosbuvir/velpatasvir ranged from being dominated (with cirrhosis) to being dominant (without cirrhosis); while for genotype 3 patients, the ICUR for GP versus sofosbuvir/velpatasvir was $99,877 per QALY (without cirrhosis) and $69,314 per QALY (with cirrhosis). In genotype 1 patients with NS5A or NS3/4A treatment experience, the ICURs for GP versus no treatment were $13,097 per QALY and $6,383 per QALY, respectively.

The results of the segment analyses indicate that GP is more cost-effective in genotype 1 treatment-naive or -experienced patients without cirrhosis than in patients with cirrhosis, due to the lengthier treatment duration in cirrhotic versus non-cirrhotic patients (12 weeks versus 8 weeks), which leads to increased total costs associated with GP therapy. In other patient populations (genotypes 2 to 6), the cost-effectiveness of GP ranges from being dominant to being a dominated treatment, based on treatment experience and presence of cirrhosis.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of limitations with the submitted analyses. Since GP was submitted to CADTH before the Health Canada Notice of Compliance was issued, the anticipated indication for GP to be reviewed by CDR was for the treatment of adult patients with chronic HCV genotype 1 through 6 (pan-genotype) in either treatment-naive or treatment-experienced patients, regardless of treatment history (NS5A, NS3/4A, or PRS).[4] Based on the final Health Canada–approved product monograph for GP, GP is indicated for use in patients who are PRS-experienced with genotype 1 to 6, but NS5A and NS3A/4A treatment experience is restricted to genotype 1 patients only.[1] The manufacturer's portfolio analysis was based on the efficacy data used in the segment analysis, where results from the individual populations were aggregated to produce the results for the full population. The segment analyses were conducted in genotypes 2, 4, 5, and 6 NS5A or NS3/4A treatment-experienced patients, despite not being indicated for these populations. CDR requested clarification on the portfolio approach submitted as part

of the manufacturer's base-case analysis, as well as on the segment analyses in genotype 1 patients with NS5A inhibitor and NS3/4A protease inhibitor treatment experience. The manufacturer's response did not address the concerns raised with the portfolio analysis, but did address the concerns with the subgroup analyses. Consequently, the portfolio approach submitted by the manufacturer was not valid, based on the Health Canada indications for GP.

Another key issue was the included efficacy parameters in the segment analysis of genotype 1 patients who had been previously treated with an NS3/4A protease inhibitor or NS5A inhibitors. These parameters were based on the MAGELLAN-1 Part 2 study[5] and were not designed or powered to test for subgroup effects. In the same analysis, the efficacy for the comparator (elbasvir/grazoprevir) was based on the C-SALVAGE study, which used an unapproved dosing for elbasvir/grazoprevir.[6] Based on the uncertainty of the comparative efficacies for GP and elbasvir/grazoprevir in this genotype 1 patient subgroup, the reported ICURs for these subgroup analyses should be considered with caution.

The sustained virologic response (SVR) rates used in the model for GP were taken from the active arms of the relevant trials. There was no formal indirect comparison of results. Instead, naive direct comparisons were conducted from pivotal clinical trials of GP and of the comparators. In some cases, the manufacturer claims a 100% SVR rate from their own trials of GP from sample sizes as small as two patients. Further, the generalizability of trial results may be limited for more complex patients, as important and common comorbidities were listed as exclusion criteria in the trials; data were scarce for with HIV coinfection, liver transplant, genotype 5 and/or 6 HCV infection, treatment-experienced genotype 3 patients, or those with prior DAA treatment experience.

CDR noted that the manufacturer did not include a disutility value for adverse events experienced by patients treated with GP or a comparator, including anemia, rash, depression, and neutropenia and thrombocytopenia. This is expected to cause bias in some results, potentially in favour of GP. However, due to the structure and technical limitations with the submitted model, a reanalysis to assess this limitation is not possible at this time.

Based on the limitations identified, CDR was limited to conducting a reanalysis of the population of genotype 1 patients who have previously been treated with an NS3/4A protease inhibitor. This reanalysis compared GP with elbasvir/grazoprevir, resulting in GP dominating elbasvir/grazoprevir.

Based on the manufacturer's segmented approach, GP appeared to be cost-effective in the following populations:

- genotype 1 and genotype 2 treatment-naive or -experienced patients without cirrhosis compared with no treatment: GP associated with ICURs below $6,000 per QALY
- genotype 1 treatment-naive patients with cirrhosis: GP dominates sofosbuvir/velpatasvir
- genotype 1 patients who were previously treated with an NS5A inhibitor: GP achieved an ICUR of $13,097 per QALY compared with no treatment
- genotype 1 patients who were previously treated with an NS3/4A inhibitor: GP achieved an ICUR of $6,383 per QALY compared with no treatment, and dominated elbasvir/grazoprevir

- genotype 3 treatment-naive patients: in patients without cirrhosis, GP is associated with an ICUR of $1,380 per QALY versus no treatment; in patients with cirrhosis, GP dominated sofosbuvir/velpatasvir.

And GP was associated with uncertainty or not cost-effective in the following:

- genotype 1 cirrhotic patients who previously experienced PRS treatment: GP dominated by sofosbuvir/velpatasvir
- genotype 2 cirrhotic patients (treatment-naive or -experienced): GP dominated by sofosbuvir/velpatasvir
- genotype 3 patients previously treated with PRS: GP achieved an ICUR of $99,877 per QALY compared with sofosbuvir/velpatasvir in patients without cirrhosis, and an ICUR of $69,314 per QALY compared with sofosbuvir/velpatasvir in patients with cirrhosis
    - in the genotype 3 population, price reductions of 7% to 12% were required to achieve an ICUR of less than $50,000 per QALY, or 15% to 18% to achieve an ICUR of less than $25,000 per QALY

No conclusions could be drawn regarding the cost-effectiveness of GP for patients with genotypes 4 or 5 or 6, due to the limited data included in the submitted model.

Conclusions

The key limitations of the submitted economic analysis as identified by CDR included use of an inappropriate model output and presentation of results, and uncertainty of clinical efficacy parameters. Although CDR attempted to address what limitations it could, the results indicate that GP is more cost-effective in genotypes 1 and 2 in treatment-naive or -experienced patients without cirrhosis than in patients with cirrhosis, due to the lengthier treatment duration in cirrhotic versus non-cirrhotic patients (12 weeks versus 8 weeks), which leads to increased total costs associated with GP therapy.

For genotypes 4 to 6, cautious consideration is warranted in light of the limited clinical data and the variability of results due to a treatment duration that is based on treatment experience and the presence or absence of cirrhosis.

Reanalyses conducted by CDR using the manufacturer's segment analyses suggest that a price reduction of 3% would be required for GP to be cost-effective for all subgroups in genotype 1 and genotype 2. For genotype 3, a price reduction ranging from 7% to 12% would be required for GP to achieve ICURs of less than $50,000 per QALY, or 15% to 18% to achieve ICURs of less than $25,000 per QALY.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis using a Markov cohort model, where patients are located in one of 13 mutually exclusive health states (Figure 1): spontaneous remission from F0 (no hepatitis C virus [HCV]), eight disease progression states (i.e., F0, F1, F2, F3; compensated cirrhosis; chronic HCV [F4]; decompensated cirrhosis [DCC]; hepatocellular carcinoma [HCC]; and liver transplant), three recovered states (i.e., SVR, history of mild disease [i.e., F0, F1]; sustained virologic response (SVR), history of moderate disease [F2 to F3]; and SVR, history of compensated cirrhosis), and absorbing mortality states (i.e., liver and non-liver death), which can be reached from any state.[3] The model structure allows patients to enter the model either as non-cirrhotic (F0 to F3) patients or in compensated cirrhosis (F4). Patients cannot initiate treatment in the DCC state. The state in which patients enter the model depend upon the particular subgroup being considered.

The manufacturer compares glecaprevir/pibrentasvir (GP) with a number of approved and funded interferon-free regimens: sofosbuvir/velpatasvir, sofosbuvir/ledipasvir, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir/dasabuvir (OBV/PTV/r/DSV), and sofosbuvir/ribavirin. The effectiveness parameters used in the model were drawn from non-comparative trials.[5,7,8] There was no formal indirect comparison of trials of relevant comparators; instead, naive direct comparisons were conducted by drawing on SVR results from individual trial arms. Baseline demographics such as genotype, treatment history, and fibrosis distributions were assessed from a Canadian market research study.[3] Fibrosis and non-fibrosis progression transitional probabilities were derived from published literature.[3] Health state health utilities were taken from published literature as well.[3] The unit costs of the comparators in the analyses were obtained from the Ontario Public Drug Programs formulary,[3] while resources such as hospitalizations, outpatient visits, diagnostic and laboratory testing, and medical procedures are based on published literature.[9,10]

The manufacturer compared the SVR rates, direct medical costs, liver outcomes, and quality-adjusted life-years (QALYs) of GP versus selected direct-acting antivirals (DAAs) such as sofosbuvir/ribavirin, sofosbuvir/velpatasvir, elbasvir/grazoprevir, sofosbuvir/ledipasvir, and ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/r/DSV). The manufacturer included two approaches for the base case: the portfolio approach in the base case (in which a pan-genotypic HCV patient population was considered), and a segmented approach (where individual patient groups were considered, with a primary focus on genotype 1–infected, non-cirrhotic, treatment-naive patients).

The model considered a lifetime horizon and was conducted from the perspective of the Canadian publicly funded health care system in the base case. Only direct costs were considered in the base case. Costs and outcomes are discounted at 1.5% per year in the base case.[3] The impact of uncertainty of model parameters was examined using probabilistic sensitivity analyses.[3]

Manufacturer's Base Case

In the manufacturer's base-case analysis using a portfolio analysis, GP was compared with sofosbuvir/ledipasvir in genotype 1 patients, sofosbuvir/ribavirin in genotype 2 patients, and sofosbuvir/velpatasvir in genotype 3 to 6 patients. The results show that GP dominated the comparators (greater QALYs and lower costs).

When considering subgroup analyses (or segment analyses) (Table 3):

- Genotype 1:
  - treatment-naive patients without cirrhosis: GP dominated (less costly and greater QALYs) all-oral DAA comparators (sofosbuvir/velpatasvir, elbasvir/grazoprevir, sofosbuvir/ledipasvir, and OBV/PTV/r/DSV), but had an incremental cost-utility ratio (ICUR) of $2,319 per QALY versus no treatment
  - treatment-naive patients with cirrhosis: GP dominated sofosbuvir/velpatasvir
  - PRS-experienced: ICUR for GP versus sofosbuvir/velpatasvir ranged from being dominated (with cirrhosis) to being dominant (without cirrhosis)
  - NS3/4A treatment experience: ICUR for GP versus no treatment was $6,383 per QALY, and GP dominated elbasvir/grazoprevir
  - NS5A treatment experience, the ICUR for GP versus no treatment was $13,097 per QALY
- Genotype 3:
  - treatment-naive patients without cirrhosis: ICUR for GP versus no treatment was $1,380 per QALY
  - treatment-naive patients with cirrhosis: GP dominated sofosbuvir/velpatasvir
  - experience with pegylated interferon plus ribavirin plus sofosbuvir (PRS) treatment: ICUR for GP versus sofosbuvir/velpatasvir was $99,877 per QALY versus sofosbuvir/velpatasvir (without cirrhosis), and $69,314 per QALY versus sofosbuvir/velpatasvir (with cirrhosis)
- For genotype 2, 4, 5, and 6:
  - treatment-naive patients without cirrhosis: ICUR for GP ranges from $2,582 to $5,891 per QALY versus no treatment
  - treatment-naive patients with cirrhosis: GP was dominated by sofosbuvir/velpatasvir
  - PRS-experienced patients without cirrhosis: ICUR for GP ranges from $1,713 to $5,919 per QALY versus no treatment
  - PRS-experienced patients with cirrhosis: GP was dominated by sofosbuvir/velpatasvir

Patients who experienced treatment failure with an NS5A-containing regimen and patients infected with HCV genotype 2, 3, 5, or 6 with chronic kidney disease (CKD) could not be assessed.

Table 3: Manufacturer's Base Case: Summary Results of the Segmented Approach

	ICUR of GP When Compared With the Following Comparators ($/QALY)					
Patient Segment	**No Treatment**	**SOF/VEL**	**EBR/GZR**	**SOF/LDV**	**OBV/PTV/r/DSV**	**SOF + RBV**
Genotype 1, TN, F0 to F3	2,319	Dominant	Dominant	Dominant	Dominant	–
Genotype 1, TN, F4	3,755	Dominant	Dominant	Dominant	5,787	–
Genotype 1, TE, F0 to F3[a]	1,492	Dominant	Dominant	Dominant	Dominant	–
Genotype 1, TE, F4[a]	4,423	**Dominated**	Dominant	(349,974)[b]	(7,033,475)[b]	–
Genotype 1, TE (NS5A), F0 to F4	13,097	–	–	–	–	–
Genotype 1, TE (NS3A/4A), F0 to F4	6,383	–	Dominant	–	–	–
Genotype 2, TN, F0 to F3	5,891	(3,634,027)[b]	–	–	–	Dominant
Genotype 2, TN, F4	3,711	**Dominated**[c]	–	–	–	1,903
Genotype 2, TE, F0 to F3[a]	5,919	(77,301)[b]	–	–	–	Dominant
Genotype 2, TE, F4[a]	3,823	**Dominated**[c]	–	–	–	Dominant
Genotype 3, TN, F0 to F3	1,380	(136,507)[b]	–	–	–	Dominant
Genotype 3, TN, F4	3,941	Dominant	–	–	–	Dominant
Genotype 3, TE, F0 to F3[a]	10,441	99,877	–	–	–	Dominant
Genotype 3, TE, F4[a]	8,531	69,314	–	–	–	Dominant
Genotype 4, TN, F0 to F3	3,633	(72,878)[b]	75,537	–	–	–
Genotype 4, TN, F4	3,751	**Dominated**[c]	Dominant	–	–	–
Genotype 4, TE, F0 to F3[a]	1,713	(10,978,774)[b]	Dominant	–	–	–
Genotype 4, TE, F4[a]	3,846	**Dominated**[c]	Dominant	–	–	–
Genotype 5, TN, F0 to F3	2,582	Dominant	–	–	–	–
Genotype 5, TN, F4	3,751	**Dominated**[c]	–	–	–	–
Genotype 5, TE, F0 to F3[a]	1,713	(10,978,774)[b]	–	–	–	–
Genotype 5, TE, F4[a]	3,846	**Dominated**[c]	–	–	–	–
Genotype 6, TN, F0 to F3	4,385	41,131	–	–	–	–
Genotype 6, TN, F4	3,751	**Dominated**[c]	–	–	–	–
Genotype 6, TE, F0 to F3[a]	1,713	(10,978,774)[b]	–	–	–	–
Genotype 6, TE, F4[a]	3,846	**Dominated**[c]	–	–	–	–

EBR/GZR = elbasvir/grazoprevir; F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; OBV/PTV/r/DSV = ombitasvir/paritaprevir/ritonavir/dasabuvir; QALY = quality-adjusted life-year; TE = treatment-experienced; TN = treatment-naive; SOF/LDV = sofosbuvir/ledipasvir; SOF + RBV = sofosbuvir and ribavirin; SOF/VEL = sofosbuvir/velpatasvir.

[a] Patients previously treated with pegylated interferon plus ribavirin plus sofosbuvir (PRS).

[b] Indicates the ICUR when GP is less costly and less effective than the comparator.

[c] Indicates an ICUR where GP results in benefits similar to the comparator but higher costs.

Source: Manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

Deterministic one-way sensitivity analyses revealed that the results are sensitive to SVR rates in both cirrhotic and non-cirrhotic patients for both GP and the comparators. The manufacturer did not report on the deterministic sensitivity analyses on the segmented approach.

Different scenario analyses were conducted by the manufacturer in the base case using the portfolio approach: varying the baseline patient characteristics and the discounting rate, considering a societal perspective, and assessing the impact of the inclusion of the costs associated with ribavirin based on the average patient weight reported in the GP phase III clinical trials. As reported by the manufacturer, GP remained the dominant option in the treatment of HCV patients with genotypes 1 to 6 compared with other available and reimbursed HCV therapies across the scenarios considered.

Limitations of Manufacturer's Submission

CDR identified a number of key limitations with the submitted analyses.

- **Invalid analysis approach.** The manufacturer presented the results of a portfolio approach that considered the overall HCV patient population (all genotypes, treatment-naive or treatment-experienced, with or without compensated cirrhosis) as their base case, as well as a segmented approach that focused on each patient segment (according to genotype, treatment history, and presence or absence of cirrhosis). Based on the approved product monograph, GP is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis, including patients with HCV genotype 1 infection who were previously treated with either a regimen consisting of an NS5A inhibitor or an NS3/4A protease inhibitor, but not both classes of inhibitors.[1] The portfolio analysis does not fully capture the approved indication, as GP is not approved for all genotypes with treatment experience. Further, the portfolio analysis is based on the efficacy data used in the segment analysis where aggregated results from the segment analyses are combined and run to produce the result of the portfolio analysis. The segment analyses, as part of the portfolio analysis, report the analyses of GP in genotypes 2, 4, 5, and 6 for either NS5A or NS3/4A treatment experience, despite not being indicated for these patient populations. Although the manufacturer had submitted revised segment analyses at CDR's request, the portfolio analysis was not updated or revised. Therefore, the focus for the review will be on the segment analyses.

- **Effectiveness parameters used in the model are drawn from non-comparative trials.** The SVR rates used in the model for GP are taken from the active arms of the relevant trials.[5,7,8] It was not possible for CDR to confirm the degree to which the patient populations were clinically comparable; therefore, it was also not possible to confirm the degree to which the estimates of differential effectiveness used in the model accurately capture the magnitude of the incremental benefit of GP. There was no formal indirect comparison of results. Instead, naive direct comparisons were conducted from pivotal clinical trials. In some cases, the manufacturer claimed a 100% SVR rate from their own trials of GP from small sample sizes (e.g., n = 2), Table 13. Generalizability of trial results may be limited for more complex patients, as important and common comorbidities were listed as exclusion criteria in the trials; data were scarce for those patients with HIV coinfection, liver transplant, genotype 5 and 6 HCV infection,

treatment-experienced genotype 3 infection, or patients with prior DAA treatment experience.

- **Efficacy parameters in segment analysis in genotype 1 patients previously treated with an NS3/4A protease inhibitor or NS5A inhibitors.** In the addendum to the manufacturer's pharmacoeconomic submission, the efficacy data for GP was based on the MAGELLAN-1 Part 2 study[5] when compared with no treatment (NS3/4A- and NS5A-experienced) and elbasvir/grazoprevir (NS3/4A-experienced). The elbasvir/grazoprevir efficacy in patients with treatment experience with NS3/4A protease inhibitors was based on the C-SALVAGE-C.[6]

  - The MAGELLAN study enrolled patients who had failed to respond to an NS3/4A protease inhibitor (30%), an NS5A inhibitor (37%) or both classes of drugs (33%).[5] Overall, the SVR 12 rate was 88.6% (95% confidence interval [CI], 76.0% to 95.0%) in patients who received GP for 12 weeks and 91.5% (95% CI, 80.1% to 96.6%) in those who received 16 weeks of treatment; however, when broken down by treatment history, all NS3/4A inhibitor–experienced patients achieved SVR 12 (100%, total N = 27), and 94% of NS5A-experienced patients achieved SVR 12.[5] As noted in the CDR clinical review for GP, although the subgroups were defined a priori, the efficacy data for GP in this patient population should be interpreted with caution, as the study was not designed or powered to test for subgroup effects.
  - The C-SALVAGE study was an open-label study of elbasvir/grazoprevir with ribavirin for 12 weeks in cirrhotic and non-cirrhotic patients with chronic HCV genotype 1 infection who had not attained SVR after treatment experience with NS3/4A protease inhibitors.[6] According to the product monograph for elbasvir/grazoprevir, elbasvir/grazoprevir over 12 weeks without ribavirin is indicated in genotype 1b patients previously treated with an NS3/4A protease inhibitor. For genotype 1a patients, the indication is elbasvir/grazoprevir plus ribavirin for 16 weeks (i.e., elbasvir/grazoprevir is not indicated for 12 weeks plus ribavirin, as reported in C-SALVAGE).[11] However, the manufacturer made an assumption that efficacy data for elbasvir/grazoprevir plus ribavirin for 12 weeks from the C-SALVAGE study may inform the SVR rate for elbasvir/grazoprevir at 12 weeks in genotype 1b patients, and the SVR rate for elbasvir/grazoprevir plus ribavirin for 16 weeks in genotype 1a patients.[3] This assumption raises uncertainty over possible over- and under-estimation of the true efficacy of elbasvir/grazoprevir distinct from the efficacy generated by ribavirin in the trial. The manufacturer also used the overall SVR rates for both genotype 1a and genotype 1b, despite the different treatment durations that lead to increased total costs with elbasvir/grazoprevir.

    1. Secondary analyses in patients with unmet medical needs. The manufacturer was unable to conduct secondary analyses in patients who experienced treatment failure with a DAA-containing regimen (no approved treatments for this subpopulation of HCV patients), and patients infected with HCV genotype 2, 3, 5, or 6 who have CKD, as currently there are no interferon- or ribavirin-free regimens suitable for use in patients infected with genotype 2, 3, 5 and 6 with CKD stage 4 and 5. However, in genotype 3 treatment-experienced patients with cirrhosis, GP resulted in an ICUR of $69,314 per QALY when compared with sofosbuvir/velpatasvir.
    2. No disutilities for adverse events. Although utility data were taken from the GP trials, the manufacturer did not assign a disutility to adverse events, including anemia, rash, depression, and neutropenia and thrombocytopenia. This may be expected to bias some results in favour of GP. Despite the availability of disutility values for adverse events such as anemia in the literature, CDR is unable to conduct a reanalysis due to the structure and technical limitations with the submitted model.

3. Uncertainty with patient demographic and distribution data. The manufacturer based the information on the demographics of patients with chronic HCV in Canada, baseline data for patient distribution across genotypes, treatment history, and fibrosis distribution based on soliciting expert opinion. Limited information is indeed available on the aforementioned parameters; however, such a limitation was not deemed critical by the CDR clinical expert on this review, as its impact is only significant in the portfolio analysis and not the segment analyses.
4. Presentation of results. The results presented by the manufacturer did not consider all comparators simultaneously in a sequential analysis. Instead, GP was compared with comparators in a pairwise manner. This method of presentation of results does not reflect best practices.

CADTH Common Drug Review Reanalyses

As noted previously, the portfolio analysis was not considered an appropriate approach and therefore was not reviewed further by CDR.

- Efficacy of elbasvir/grazoprevir in genotype 1 patients previously treated with an NS3/4A protease inhibitor: CDR conducted a reanalysis of GP compared with elbasvir/grazoprevir using genotype subgroup efficacy data for elbasvir/grazoprevir from the C-SALVAGE study. In the manufacturer's model, the SVR for elbasvir/grazoprevir was 96.1% (76 out of 79) for both genotype 1a and genotype 1b subgroups; CDR's reanalysis applied an SVR of 93% (28 out of 30) in the genotype 1a subgroup and 98% (48 out of 49) in the genotype 1b patients. The results of the analysis are presented in Table 4.

Table 4: Summary of Results of CDR Reanalysis

	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	ICUR ($/QALY)
EBR/GZR	75,852		19.154		
GP	74,272	−1,579	19.067	0.087	Dominant

CDR = CADTH Common Drug Review; EBR/GZR = elbasvir/grazoprevir; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Price Reduction Analyses

A series of price reduction analyses were undertaken based on the manufacturer's segment analyses and the CDR's base-case result in genotype 1 patients who have treatment experience with an NS3A/4A protease inhibitor (Table 5).

Table 5: Summary of Price Reduction Analyses

	Base ICUR ($/QALY)	Reduction Required	Revised ICUR ($/QALY)
Manufacturer Base-Case Results	**GP Versus SOF/VEL**		
Genotype 1, TE, F4[a]	Dominated	**3%**	(2,389)[b]
Genotype 2, TN, F4	Dominated[c]	**3%**	Dominant[d]
Genotype 2, TE, F4[a]			
Genotype 3, TE, F0 to F3[a]	99,877	**12%**	48,627
		18%	23,001
Genotype 3, TE, F4[a]	69,314	**7%**	48,228
		15%	24,130
Genotype 4, TN, F4	Dominated[c]	**1%**	Dominant[d]
Genotype 4, TE, F4[a]	Dominated[c]		
Genotype 5, TN, F4	Dominated[c]		
Genotype 5, TE, F4[a]	Dominated[c]		
Genotype 6, TN, F4	Dominated[c]		
Genotype 6, TE, F4[a]	Dominated[c]		

F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = pegylated interferon plus ribavirin plus sofosbuvir; QALY = quality-adjusted life-year; SOF/VEL = sofosbuvir/velpatasvir; TE = treatment-experienced; TN = treatment-naive.

[a] Patients previously treated with PRS.

[b] Indicates the ICUR when GP is less costly and less effective than the comparator.

[c] Indicates an ICUR where GP results in benefits similar to comparator but with higher costs.

[d] Indicates an ICUR where GP results in benefits similar to comparator but with lower costs.

Patient Input

According to patient group input received by CDR for this submission from the Canadian Liver Foundation, Canadian Treatment Action Council, the Pacific Hepatitis C Network, and the Hepatitis C Education and Prevention Society, symptoms of HCV infection vary widely, with some patients having few or no symptoms, and others experiencing fatigue, abdominal, muscle or joint pain, poor circulation, constipation, diarrhea, nausea, headaches, loss of appetite, sensitivity to light or food, psoriasis, peripheral neuropathy, osteopenia, disrupted sleep, and jaundice. In some patients, the disease affects cognitive function and memory. Fatigue and other symptoms may be severe and can limit a patient's ability to work, care for family members, and maintain friendships. The utilities applied in the submitted model likely capture the impact of such symptoms on quality of life to some extent, but may not be reflective of the full spectrum of symptom severity experienced by real-world patients, as the analysis is based on modelling SVR and not the symptoms themselves.

Spouses and caregivers of patients with HCV infection are faced with a substantial burden, as the symptoms of HCV infection can leave the patient dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children. The submitted model's base-case analysis only reflects costs to the health care system and the clinical effects experienced by the patient. An analysis from the societal perspective is provided as a scenario analysis.

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 GP in patients coinfected with HIV.

Regimen complexity was described by patient groups as a potential barrier to effective treatment of HCV infection, particularly in relation to treatment adherence. The submitted model was based on SVR rates observed in clinical trials, which may not necessarily reflect real-world effectiveness.

Issues for Consideration

- Previously, DAA treatments for HCV infections reviewed by the CADTH Canadian Drug Expert Committee (CDEC) were recommended for reimbursement at reduced prices.[12-16] Therefore, the cost-effectiveness results for GP have the potential to vary with possible lower costs of comparators.
- Sofosbuvir/velpatasvir/voxilaprevir (Vosevi), indicated for the treatment of chronic HCV infection in adult patients without cirrhosis or with compensated cirrhosis is currently being reviewed by CDR.[17]

Conclusions

The key limitations of the submitted economic analysis as identified by CDR included use of an inappropriate model output and presentation of results, and uncertainty of clinical efficacy parameters. Although CDR attempted to address what limitations it could, the results indicate that GP is more cost-effective in genotypes 1 and 2 in treatment-naive or –experienced patients without cirrhosis than in patients with cirrhosis, due to the lengthier treatment duration in cirrhotic versus non-cirrhotic patients (12 weeks versus 8 weeks), which leads to increased total costs associated with GP therapy.

For genotypes 4 to 6, cautious consideration is warranted in light of the limited clinical data and the variability of results due to a treatment duration that is based on treatment experience and the presence or absence of cirrhosis.

Reanalyses conducted by CDR using the manufacturer's segment analyses suggest that a price reduction of 3% would be required for GP to be cost-effective for all subgroups in genotype 1 and genotype 2. For genotype 3, a price reduction ranging from 7% to 12% would be required for GP to achieve ICURs of less than $50,000 per QALY, or 15% to 18% to achieve ICURs of less than $25,000 per QALY.

Appendix 1: Cost Comparison

The comparators presented in the Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in Table 6 and, as such, may not represent the actual costs to public drug plans.

Table 6: CDR Cost Comparison Table for Drugs Indicated for Hepatitis C Virus Genotype 1

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combo Therapy ($)
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	**Tab**	**714.2900[a]**	**300 mg/120 mg daily**	**8 weeks[b]**	**40,000**	**40,000**
					12 weeks[c]	**60,000**	**60,000**
					16 weeks[d]	**80,000**	**80,000**
Interferon-free regimens							
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tab	714.285[e]	1 tablet daily	12 weeks[f]	**60,000**	**60,000**
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi)	60 mg	Tab	428.5714	60 mg daily	12 weeks[f,g]	36,000	83,000
	400 mg	Tab	654.7619	400 mg daily		55,000	
Daclatasvir (Daklinza) plus asunaprevir (Sunvepra) (genotype 1b)	60 mg	Tab	428.5714	60 mg daily	24 weeks	72,000	NA
	100 mg	Tab	NA	100 mg twice daily		NA	
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) plus RBV	60 mg	Tab	428.5714	60 mg daily	12 weeks[h]	36,000	94,045 to 94,654
	400 mg	Tab	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tab	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	Tab	666.9400	50 mg/100 mg daily	12 weeks[i]	56,023	56,023
Elbasvir/grazoprevir (Zepatier) plus RBV	50 mg/100 mg	Tab	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 ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combo Therapy ($)
Ledipasvir/sofosbuvir (Harvoni)	90 mg/400 mg	Tab	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	Tabs	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	Tabs	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 to 1,200 mg daily			
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tab	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 to 1,200 mg daily		6,090 to 7,308	
Sofosbuvir/velpatasvir (Epclusa)	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[o]	12 weeks	60,000	60,000
Sofosbuvir/velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[o]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[o]		3,045 to 3,654	
Simeprevir (Galexos) plus sofosbuvir (Sovaldi)	150 mg	Cap	434.5500	150 mg daily	12 to 24 weeks[p]	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
Direct-acting antivirals in combination with pegylated interferon alpha plus ribavirin therapy							
Daclatasvir plus asunaprevir plus PR	60 mg	Tab	428.5714	60 mg daily	24 weeks	72,000	NA
	100 mg	Tab	NA	100 mg twice daily		NA	

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combo Therapy ($)
	180 mcg/200 mg	Vial/tab	407.3900	60 mg daily plus 100 mg twice daily + Peg-IFN 180 mcg/wk; RBV 800 mg to 1,200 mg per day		9,777	
Sofosbuvir (Sovaldi) plus PR	400 mg	Tab	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg/200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/wk; RBV 1,000 to 1,200 mg daily		4,889	
Simeprevir (Galexos) plus PR	150 mg	Cap	434.5500	150 mg daily	12 weeks	36,502	46,279 to 56,057
	180 mcg/200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/wk; RBV 800 mg to 1,200 mg per day	24 to 48 weeks[q]	9,777 to 19,555	
Boceprevir (Victrelis) plus PR	200 mg	Cap	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
	120 mcg/200 mg	Pens/ caps	876.7800	Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg per day[o]	28 to 48 weeks	12,275 to 21,043	
Boceprevir/ Peg-IFN alfa-2b + RBV (Pegetron) (Victrelis Triple)	200 mg/80 mcg/ 200 mg 200 mg/100 mcg/ 200 mg 200 mg/120 mcg/ 200 mg 200 mg/150 mcg/ 200 mg	168 caps + 2 pens + 56 caps	2652.5500[r] 2652.5500[r] 2726.0000[r] 2726.0000[r]	Boceprevir 800 mg three times daily; peg-IFN 1.5 mcg/kg/wk; RBV 800 mg to 1,400 mg per day, initiated after 4 weeks of Pegetron therapy	24 to 44 weeks[s]	31,831 to 59,972	31,831 to 59,972
Pegylated interferon alpha plus ribavirin therapy							
Peg-IFN alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe / 28 tabs 35 tabs 42 tabs	407.3900	Peg-IFN 180 mcg/wk; RBV 1,000 mg to 1,200 mg per day[j]	48 weeks	19,555	19,555
Peg-IFN alfa-2b + RBV (Pegetron)	50 mcg/200 mg	2 vials + 56 caps	793.4700[r]	Peg-IFN 1.5 mcg/kg/wk; RBV 800 mg to 1,400 mg per day	48 weeks	19,043	19,043
	150 mcg/200 mg	2 vials + 84 or 98 caps	876.7800[r]			21,043	21,043

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combo Therapy ($)
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

cap = capsule; CDR = CADTH Common Drug Review; HCV = hepatitis C virus; IFN = interferon; NA = not available; NS = nonstructural viral protein; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid; tab = tablet; wk = week.

All prices are from the Saskatchewan Drug Plan online formulary (July 2017), unless otherwise indicated.[18]

[a] Manufacturer's submitted price as of October 2017.[19]

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

[c] Twelve weeks for all treatment-naive patients with cirrhosis, or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors with cirrhosis.

[d] Sixteen weeks for all treatment-experienced genotype 3 patients and genotype 1, 2, 4, 5, and 6 patients with NS5A inhibitor experience.

[e] DeltaPA. QuintilesIMS (October 2017).[20]

[f] Twelve weeks for patients with: genotype 1, 2, 3, 4, 5, or 6 infection and who have been treated previously with an NS5A inhibitor; genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir, without an NS5A inhibitor.

[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] Twelve weeks for genotype 1 treatment-naive and treatment-experienced relapsers, and genotype 1b treatment-experienced patients with on-treatment virologic failure. Eight weeks can be considered in genotype 1b treatment-naive patients without significant fibrosis or cirrhosis.

[j] For genotype 1a patients with treatment-experienced on-treatment virologic failure.

[k] Twelve weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. Eight weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

[l] List price is $665 per daily dose. Moderiba brand RBV is reimbursed at 0.0001 per tablet when used by Holkira Pak patients. When not provided free of charge, a 12- to 24-week course of RBV would cost $3,045 to $7,308 per patient.

[m] Twelve weeks of Holkira Pak alone for patients with genotype 1b, without cirrhosis or with compensated cirrhosis; 12 weeks of Holkira Pak plus RBV for patients with genotype 1a, without cirrhosis or with compensated cirrhosis; ; 24 weeks of Holkira Pak plus RBV for patients with genotype 1a with cirrhosis who had previous null response to Peg-IFN and RBV.

[n] For treatment-naive and treatment-experienced non-cirrhotic patients with genotype 1 who are ineligible to receive an IFN.

[o] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus RBV in patients with decompensated cirrhosis.

[p] Twelve weeks for treatment-naive, prior-relapse patients, or prior nonresponders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.

[q] Twenty-four weeks for treatment-naive or prior-relapse patients with or without cirrhosis without HIV coinfection, or without cirrhosis but with HIV coinfection. Forty-eight weeks for treatment-naive or prior-relapse patients with cirrhosis and HIV coinfection. Forty-eight weeks for prior nonresponders with or without cirrhosis and with or without HIV coinfection.

[r] Ontario Drug Benefit Exceptional Access Program (July 2017).[21]

[s] Treatment duration is response-guided, based on viral load.

Table 7: Cost Comparison Table for Drugs Indicated for Hepatitis C Virus Genotype 2

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Glecaprevir/pibrentasvir (Maviret)	100 mg/40 mg	**Tab**	**714.2900**[a]	**300 mg/ 120 mg daily**	**8 weeks**[b]	**40,000**	**40,000**
					12 weeks[c]	**60,000**	**60,000**
					16 weeks[d]	**80,000**	**80,000**
Interferon-free regimens							
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tab	714.2857[e]	1 tablet daily	12 weeks[f]	**60,000**	**60,000**
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi)	60 mg	Tab	428.5714	60 mg daily	12 weeks[g]	36,000 to 72,000	83,000 to 138,000
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) plus RBV	60 mg	Tab	428.5714	60 mg daily	12 weeks[h]	36,000	94,045 to 94,654
	400 mg	Tab	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tab	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	Tab	654.7619	400 mg daily	12 weeks	55,000	58,045 to 58,654
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Sofosbuvir/velpatasvir (Epclusa)	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[i]	12 weeks	60,000	**60,000** **63,045 to 63,654**
Sofosbuvir/velpatasvir (Epclusa) plus RBV	400/100 mg	Tab	714.2857	400 mg/100 mg daily[i]	12 weeks	60,000	
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[i]		3,045 to 3,654	

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Pegylated interferon alpha plus ribavirin therapy							
Peg-IFN alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe/ 28 tabs 35 tabs 42 tabs	407.3900	Peg-IFN 180 mcg/week; RBV 1,000 mg to 1,200 mg per day	48 weeks	19,555	19,555
Peg-IFN alfa-2b + RBV (Pegetron)	50 mcg/200 mg	2 vials + 56 caps	793.4700[j]	Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg per day	48 weeks	19,043	19,043
	150 mcg/200 mg	2 vials + 84 or 98 caps	876.7800[j]			21,115	21,115
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	802.9900 802.9900 887.3000 887.3000			19,043 to 21,115	19,043 to 21,115

cap = capsule; NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; tab = tablet.
All prices are from the Saskatchewan Drug Plan online formulary (July 2017) unless otherwise indicated.[18]
[a] Manufacturer's submitted price as of October 2017.[19]
[b] 8 weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors without cirrhosis.
[c] 12 weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors with cirrhosis.
[d] 16 weeks for all treatment-experienced genotype 3 patients and genotype 1, 2, 4, 5, and 6 patients with NS5A inhibitor experience.
[e] DeltaPA. QuintilesIMS (October 2017).[20]
[f] 12 weeks for genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an NS5A inhibitor; genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
[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 sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. 12 weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.
[j] Ontario Drug Benefit Exceptional Access Program (July 2017).[21]

Table 8: Cost Comparison Table for Drugs Indicated for Hepatitis C Virus Genotype 3

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	**Tab**	**714.2900**[a]	**300 mg/120 mg daily**	**8 weeks**[b]	**40,000**	**40,000**
					12 weeks[c]	**60,000**	**60,000**
					16 weeks[d]	**80,000**	**80,000**
Interferon-free regimens							
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tab	714.2857[e]	1 tablet daily	12 weeks[f]	**60,000**	**60,000**
Daclatasvir (Daklinza) plus Sovaldi	60 mg	Tab	428.5714	60 mg daily	12 weeks[g]	36,000 to 72,000	91,000 to 182,000
	400 mg	cap	654.7619	400 mg daily		55,000 to 110,000	
Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) plus RBV	60 mg	Tab	428.5714	60 mg daily	12 weeks[h]	36,000	94,045 to 94,654
	400 mg	Tab	654.7619	400 mg daily		55,000	
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily		3,045 to 3,654	
Elbasvir/grazoprevir (Zepatier) plus sofosbuvir (Sovaldi)	100 mg/50 mg	Tab	666.9400	50/100 mg daily	12 weeks	56,023	111,023
	400 mg	Cap	654.7619	400 mg daily		55,000	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tab	654.7619	400 mg daily	24 weeks	110,000	116,090 to 117,308
	400 mg 600 mg	Cap	14.5000 21.7500	1,000 mg to 1,200 mg daily		6,090 to 7,308	
Sofosbuvir/velpatasvir Epclusa)	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[i]	12 weeks	60,000	60,000

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Sofosbuvir/velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[i]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[i]		3,045 to 3,654	
Pegylated interferon alpha plus ribavirin therapy							
Peg-IFN alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe / 28 tabs 35 tabs 42 tabs	407.3900	Peg-IFN 180 mcg/week; RBV 1,000 mg to 1,200 mg per day	48 weeks	19,555	19,555
Peg-IFN alfa-2b + RBV (Pegetron)	50 mcg /200 mg	2 vials + 56 caps	793.4700[j]	Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg per day	48 weeks	19,043	19,043
	150 mcg/ 200 mg	2 vials + 84 or 98 caps	876.7800[j]			21,043	21,043
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

HCV = hepatitis C virus; NA = not available; NS = nonstructural viral protein; peg-IFN = pegylated interferon; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (July 2017) ,unless otherwise indicated.[18]
[a] Manufacturer's submitted price as of October 2017.[19]
[b] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors without cirrhosis.
[c] Twelve weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors with cirrhosis.
[d] Sixteen weeks for all treatment-experienced genotype 3 patients and genotype 1, 2, 4, 5, and 6 patients with NS5A inhibitor experience.
[e] DeltaPA. QuintilesIMS (October 2017).[20]
[f] Twelve weeks for patients with genotype 1, 2, 3, 4, 5, or 6 infection that have been previously treated with an NS5A inhibitor, and patients with genotype 1, 2, 3, or 4 infection that have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
[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] Twelve weeks sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.
[j] Ontario Drug Benefit Exceptional Access Program (July 2017).[21]

Table 9: Cost Comparison Table for Drugs Indicated for Hepatitis C Virus Genotype 4

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	**Tab**	**714.2900**[a]	**300 mg/120 mg daily**	**8 weeks**[b]	**40,000**	**40,000**
					12 weeks[c]	**60,000**	**60,000**
					16 weeks[d]	**80,000**	**80,000**
Interferon-free regimens							
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tab	714.2857[e]	1 tablet daily	12 weeks[f]	**60,000**	**60,000**
Elbasvir/grazoprevir (Zepatier)	50 mg/100 mg	Tab	666.9400	50 mg/100 mg daily	12 weeks[g]	56,023	60,300
Elbasvir/grazoprevir (Zepatier) plus RBV	100 mg/50 mg	Tab	666.9400	50 mg/100 mg daily	16 weeks[h]	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	Tab	665.0000 per two tabs	25 mg/150 mg/ 100 mg daily	12 weeks[g]	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	Cap	434.5500	150 mg daily	12 to 24[i] weeks	36,502 to 73,004	91,502 to 183,004
	400 mg	Tab	654.7619	400 mg daily		55,000 to 110,000	
Sofosbuvir/velpatasvir (Epclusa)	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[j]	12 weeks	60,000	60,000
Sofosbuvir/velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[j]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[j]		3,045 to 3,654	
Direct-acting antivirals in combination with pegylated interferon alpha plus ribavirin therapy							
Daclatasvir (Daklinza) plus Asunaprevir (Sunvepra) plus PR	60 mg	Tab	428.5714	60 mg daily	24 weeks	72,000	NA
	100 mg	Tab	NA	100 mg twice daily		NA	
	180 mcg/200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day		9,777	

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Sovaldi (sofosbuvir) plus PR	400 mg	Tab	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg/200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day		4,889	
Simeprevir (Galexos) plus PR	150 mg	Cap	434.5500	150 mg daily	12 weeks	36,502	56,057
	180 mcg/200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day	48 weeks[k]	19,555	
Pegylated interferon alpha plus ribavirin therapy							
Peg-IFN alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe / 28 tabs 35 tabs 42 tabs	407.3900	Peg-IFN 180 mcg/week; RBV 1,000 mg to 1,200 mg/day[i]	48 weeks	19,555	19,172
Peg-IFN alfa-2b + RBV (Pegetron)	50 mcg/200 mg	2 vials + 56 caps	793.4700[l]	Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day	48 weeks	19,043	19,043
	150 mcg/200 mg	2 vials + 84 or 98 caps	876.7800[l]			21,043	21,043
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

HCV = hepatitis C virus; NA = not available; NS = nonstructural viral protein; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (July 20, 2017) unless otherwise indicated.[18]
[a] Manufacturer's submitted price as of October 2017.[19]
[b] Eight weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors without cirrhosis.
[c] Twelve weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors with cirrhosis.
[d] Sixteen weeks for all treatment-experienced genotype 3 patients and genotype 1, 2, 4, 5, and 6 patients with NS5A inhibitor experience.
[e] DeltaPA. QuintilesIMS (October 2017).[20]
[f] Twelve weeks for patients with genotype 1, 2, 3, 4, 5, or 6 infection who have previously been treated with an NS5A inhibitor, and patients with genotype 1, 2, 3, or 4 infection who have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
[g] Twelve weeks for genotype 4 treatment-naive and treatment-experienced relapsers.
[h] For genotype 4 patients with treatment-experienced on-treatment virologic failure.
[i] Twelve weeks for treatment-naive, prior-relapse patients, or prior nonresponders with or without cirrhosis who are not coinfected with HIV. Treatment of up to 24 weeks should be considered for patients with cirrhosis.
[j] Twelve weeks of sofosbuvir/velpatasvir alone for patients without cirrhosis and patients with compensated cirrhosis. Twelve weeks of sofosbuvir/velpatasvir plus ribavirin in patients with decompensated cirrhosis.
[k] Forty-eight weeks for genotypes 1 and 4. RBV dose of 800 mg daily recommended for patients with HIV coinfection.
[l] Ontario Drug Benefit Formulary Exceptional Access Program (July 2017).[21]

Table 10: Cost Comparison Table for Drugs Indicated for Hepatitis C Virus Genotypes 5 and 6

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Glecaprevir/ pibrentasvir (Maviret)	100 mg/40 mg	**Tab**	**714.2900[a]**	**300 mg/120 mg daily**	**8 weeks[b]**	**40,000**	**40,000**
					12 weeks[c]	**60,000**	**60,000**
					16 weeks[d]	**80,000**	**80,000**
Interferon-free regimens							
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	400 mg/100 mg/ 100 mg	Tab	714.2857[e]	1 tablet daily	12 weeks[f]	**60,000**	**60,000**
Ledipasvir / Sofosbuvir (Harvoni)[g]	90 mg/400 mg	Tab	797.6190	90 mg/400 mg daily	12 weeks	67,000	67,000
Sofosbuvir velpatasvir (Epclusa)	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[h]	12 weeks	60,000	60,000
Sofosbuvir/velpatasvir (Epclusa) plus RBV	400 mg/100 mg	Tab	714.2857	400 mg/100 mg daily[h]	12 weeks	60,000	63,045 to 63,654
	200 mg 400 mg 600 mg	Tab	7.2500 14.5000 21.7500	1,000 mg to 1,200 mg daily[h]		3,045 to 3,654	
	400 mg 600 mg	Cap	14.5000 21.7500	1,000 mg to 1,200 mg daily		6,090 to 7,308	
Direct-acting antivirals in combination with Pegylated interferon alpha plus ribavirin therapy							
Sovaldi (sofosbuvir) plus PR[d]	400 mg	Tab	654.7619	400 mg daily	12 weeks	55,000	59,889
	180 mcg /200 mg	Vial/tab	407.3900	Peg-IFN 180 mcg/week; RBV 800 mg to 1,200 mg/day		4,889	

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)	Total Cost for One Course of Combination Therapy ($)
Pegylated interferon alpha plus ribavirin therapy							
Peg-IFN alfa-2a + RBV (Pegasys RBV)	180 mcg /200 mg	Vial or syringe/ 28 tabs 35 tabs 42 tabs	407.3900	Peg-IFN 180 mcg/week; RBV 1,000 mg to 1,200 mg/day	48 weeks	19,555	19,555
Peg-iFN alfa-2b + RBV (Pegetron)	50 mcg /200 mg	2 vials + 56 caps	793.4700	Peg-IFN 1.5 mcg/kg/week; RBV 800 mg to 1,400 mg/day	48 weeks	19,043	19,043
	150 mcg/ 200 mg	2 vials + 84 or 98 caps	876.7800			21,043	21,043
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 pens / 56 to 98 caps	802.9900 802.9900 887.3000 887.3000			19,272 to 21,295	19,272 to 21,295

NA = not available; peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin;
RBV = ribavirin.
All prices are from the Saskatchewan Drug Plan online formulary (July 2017) unless otherwise indicated.[18]
[a] Manufacturer's submitted price as of October 2017.[19]
[b] 8 weeks for all treatment-naive patients without cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors without cirrhosis.
[c] 12 weeks for all treatment-naive patients with cirrhosis or genotype 1, 2, 4, 5, and 6 treatment-experienced patients naive to NS5A inhibitors with cirrhosis.
[d] 16 weeks for all treatment-experienced genotype 3 patients and genotype 1, 2, 4, 5, and 6 patients with NS5A inhibitor experience.
[e] DeltaPA. QuintilesIMS (October 2017).[20]
[f] 12 weeks for genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an NS5A inhibitor.
[g] Not indicated, however recommended for genotype 6 only in the 2015 Consensus Guidelines from the Canadian Association for the Study of the Liver.[22]
[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.

Appendix 2: Additional Information

Table 11: 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 12: Authors' Information

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review

☐ Adaptation of global model / Canadian model done by the manufacturer

☒ Adaptation of global model / Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model / Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

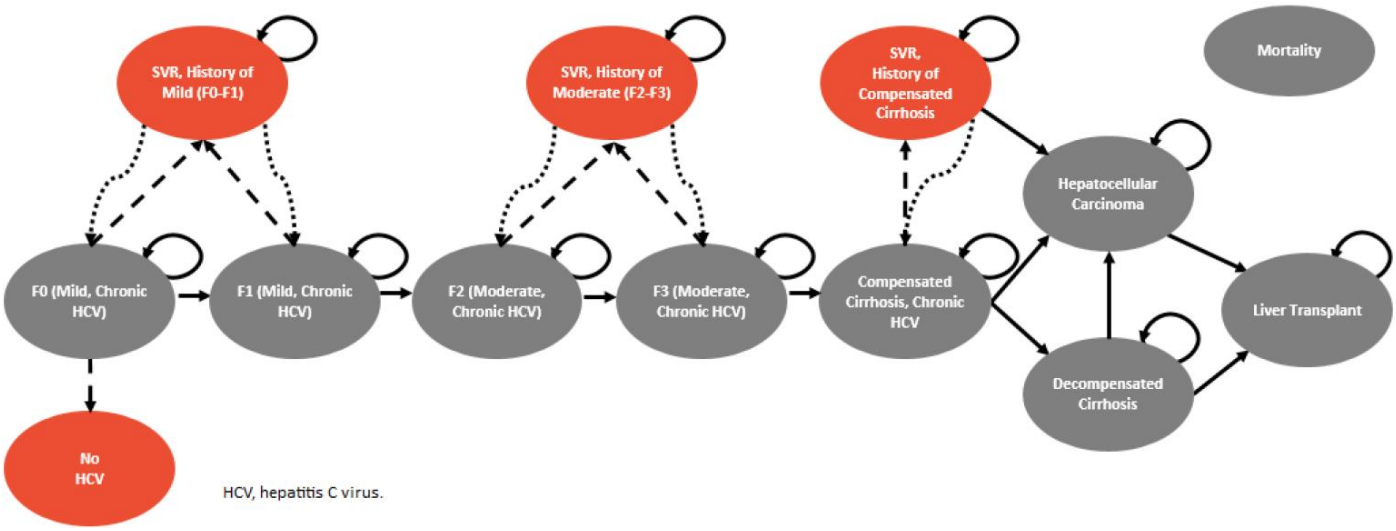
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

Appendix 3: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer's model was based on previously published models of the natural history of chronic hepatitis C virus (HCV) infection, including Liu et al. (2012)[23] and Brady et al. (2007).[10] The model was also based on a previous model which the manufacturer had submitted to CADTH for Holkira Pak (ombitasvir/paritaprevir/ritonavir [OBV/PTV/r/DSV]).[24] Most notably, the structure of the OBV/PTV/r/DSV model was updated to permit disease progression by METAVIR (fibrosis) stages: patients enter the model and initiate treatment through one of five initial fibrosis states (i.e., F0, F1, F2, F3, and F4). Patients cannot initiate treatment in the decompensated cirrhosis (DCC) state. The same natural history model to capture lifetime disease progression of HCV patients was applied by the manufacturer regardless of treatment history (i.e., treatment-naive or -experienced) and genotype (i.e., genotype 1 to 6). The Markov model structure is presented in Figure 1.

Figure 1: Schematic of Manufacturer's Pharmacoeconomic Model



Source: Manufacturer's pharmacoeconomic submission.[3]

The natural history model is made up of 13 health states, including: spontaneous remission from F0 (no HCV), eight disease progression states (i.e., F0; F1; F2; F3; compensated cirrhosis, chronic HCV [F4]; DCC; hepatocellular carcinoma [HCC]; and liver transplant), three recovered states (i.e., sustained virologic response [SVR], history of mild disease [i.e., F0, F1]; SVR, history of moderate disease [F2 to F3]; and SVR, history of compensated cirrhosis), and absorbing mortality states (i.e., liver and non-liver death), which can be reached from any state. DCC is modelled as one health state. The manufacturer noted the presence of clinical data to support that SVR suspends liver fibrosis progression,[3] as well as the designation of SVR as a reliable surrogate for long-term clinical outcomes and, accordingly, to assume that attainment of SVR will reduce the probability of morbidity and mortality.[3]

Patients who do not achieve SVR are at risk of progressive liver disease and are assumed to face the same risks of disease progression as untreated patients. In the absence of

successful treatment, patients may remain in their existing health state or may progress to more severe stages of liver disease following natural disease progression. A proportion of patients with compensated cirrhosis progresses to DCC and HCC. Some patients with DCC progress to HCC, while a proportion receive liver transplants. Patients with HCC may also receive liver transplants (e.g., Brady et al. [2007][10] and Liu et al. [2012][23]). Finally, it was assumed in the base case that spontaneous remission is not possible for patients with chronic HCV, setting transition probability from F0 to no HCV to zero.[3] Achievement of SVR (successful treatment) results in patients transitioning to recovered states. Patients who are reinfected transition back to the same fibrosis state prior to achieving SVR.

The manufacturer's model stratifies patients who achieve SVR (i.e., those who transition to recovered health states) by fibrosis severity (i.e., mild [F0 to F1], moderate [F2 to F3], and compensated cirrhosis [F4]), consistent with Brady et al. (2007).[10] This accounts for differential risks faced by patients with different disease histories: patients who achieve SVR from mild or moderate chronic HCV are assumed to face no remaining excess risk of HCC, whereas those who achieve SVR from compensated cirrhosis are assumed to still face a remaining risk of HCC. For patients who achieve SVR, HCV reinfection is possible; therefore, reinfected patients were assumed to transition back to their respective fibrosis state prior to achieving SVR.

In patients without cirrhosis, mortality risk is assumed to be the same as that of the Canadian general population (based on Statistics Canada mortality rates).[3] In patients with compensated cirrhosis, mortality risk is also assumed to be the same as that of the general population, except that patients may develop HCC.[3] Last, the states represented by more advanced liver disease, namely DCC, HCC, and liver transplant, carry excess liver-related mortality risks.[3]

For the demographics of patients with chronic HCV in Canada, baseline data on genotype distribution, treatment history, and fibrosis distribution were estimated from a Canadian market research study, the Adelphi Patient Tracking Study,[3] an online survey conducted by the manufacturer on the management of HCV-infected patients, including the treatment regimens being used.[3]

The SVR rates used in the model for glecaprevir/pibrentasvir (GP) are taken from the active arms of the relevant trials.[5,7,8] There was no formal indirect comparison of results. Instead, naive direct comparisons were conducted from pivotal clinical trials. In some cases, the manufacturer claimed a 100% SVR rate from their own trials of GP from small sample sizes (e.g., n = 2) (Table 13.)

Table 13: Disaggregated SVR Rates From the Glecaprevir/Pibrentasvir Trials Used in the Manufacturer's Model

	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
TN NC	207/209	172/174	149/157	36/39	2/2	7/8
TN CC	66/66	24/24	63/64	12/12	2/2	6/6
TE (PRS) NC	125/126	21/23	21/22	9/9	9/9	9/9
TE (PRS) CC	22/23	7/7	48/51	5/5	5/5	5/5
NS5A-experienced (NC or CC)	16/17	–	–	–	–	–
NS3/4A-experienced (NC or CC)	14/14	–	–	–	–	–

CC = compensated cirrhosis; ICUR = incremental cost-utility ratio; NC = non-cirrhotic; NS = nonstructural protein; PRS = pegylated interferon plus ribavirin plus sofosbuvir; SVR = sustained virological response; TE = treatment-experienced; TN = treatment-naive.

Treatment-related health utility was derived from the EuroQol 5-Dimensions (EQ-5D) 3-Levels (EQ-5D-3L) questionnaire used in the phase III GP trials, while the phase II SURVEYOR-II trial employed the 5-Levels questionnaire (EQ-5D-5L). Enrolled patients completed an EQ-5D questionnaire prior to drug administration (on day 1, i.e., baseline visit) and prior to any discussion of adverse events or any review of laboratory findings, including HCV ribonucleic acid (RNA) levels.[3] Treatment-related health-utility data were derived from published literature for the comparator regimens, where available. Where no data on treatment-related health utility exist, the manufacturer made simplifying assumptions using available data.

Table 14: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	The effectiveness estimates (SVR rates) were taken from the active intervention arms of pivotal trials.	There is a high potential for bias in the estimates produced by observed SVR rates in the clinical trials. Uncertainty in SVR estimates were not appropriately captured in the model.
Natural history	The natural history model of HCV was based on previously published cost-effectiveness models (Brady et al. [2007]; Hartwell et al. [2011], Liu et al. [2012], and Johnson et al. [2016]).[3]	The model by Liu et al. (2012), that employs a structure that simulates HCV disease progression through METAVIR stages (i.e., F0, F1, F2, F3, and F4), was used by the manufacturer.[3]
Utilities	Treatment-related health utility was derived from the EQ-5D-3L instrument used in the phase III GP trials and from the EQ-5D-5L used in the phase II SURVEYOR-II trial. Treatment-related health-utility data were derived from published literature for the comparator regimens.[3]	The utilities for adverse events were not considered.
Resource use	The manufacturer considered costs for health states, drug acquisition, and adverse events. The model also considered utilization of other resources such as hospitalizations, outpatient visits, diagnostic and laboratory testing, and medical procedures.[3]	The costs associated with the monitoring of therapies were not included, as these costs were assumed to be similar among GP and the other available HCV therapies.
Adverse events (Indicate which specific adverse events were considered in the model.)	The model considered five adverse events: anemia, depression, rash, grade 3 or 4 neutropenia, and grade 3 or 4 thrombocytopenia.	This approach is consistent with several prior CADTH reviews.
Mortality	Age- and gender-specific mortality rates were taken from Health Canada. Annual background mortality was applied to patients in all health states. Excess mortality data were applied to the decompensated cirrhotic, transplant, and hepatocellular cancer states.	
Costs		
Drug	The unit cost of HCV therapies was obtained from the Ontario Public Drug Programs Formulary.[3]	The cost of ribavirin was not considered in the base case. In scenario analyses, the cost of ribavirin was included based on an average patient baseline weight as reported in the GP phase III clinical trials.[3]

Data Input	Description of Data Source	Comment
Adverse events	RAMQ database study by Lachaine et al.(2014)[3] for anemia, rash, and depression. Costs related to grade 3 or 4 neutropenia and thrombocytopenia are based on the Ontario Case Costing Initiative.[21]	Majority (95.2%) of patients included in the Lachaine study were treated with PR only, which means that duration of PR exposure (and associated anemia and costs) was longer (48 weeks) than what is likely to be observed in current practice.[3]
Health state	The costs were based on Brady et al. (2007),[10] except for the costs of DCC, which were from Krahn et al. (2005).[9]	It is unclear how the costs associated with monitoring SVR were assumed in the model.

DCC = decompensated cirrhosis; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; RAMQ = PR= pegylated interferon plus ribavirin; Régie de l'assurance maladie du Québec; SVR = sustained virologic response.

Table 15: Manufacturer's Key Assumptions

Assumption	Comment
Patients who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risks of disease progression as untreated patients.	Appropriate.
Spontaneous remission is not possible for patients with chronic HCV, therefore setting transition probability from F0 to no HCV to zero.	Likely inappropriate. Although this is a conservative assumption by the manufacturer justified by the absence of data, expert opinion suggests that remission is witnessed in clinical practice but does require further research.
Patients who achieve SVR from mild or moderate chronic HCV are assumed to face no remaining excess risk of HCC, whereas those who achieve SVR from compensated cirrhosis are assumed to still face remaining risk of HCC.	Likely appropriate as suggested by expert opinion.
HCV reinfected patients are assumed to transition back to their respective fibrosis state prior to achieving SVR.	Uncertain. Manufacturer based this assumption on expert opinion.
No utilities are assessed for adverse events.	Assuming that adverse events do not affect patient utilities may bias results.

HCC = hepatocellular carcinoma; HCV = hepatitis C virus; SVR = sustained virologic response.

Manufacturer's Results

Base Case: Portfolio Approach

In the portfolio approach of the base case, the manufacturer assessed the cost-effectiveness of GP in genotypes 1 to 6 versus a comparator portfolio comprising sofosbuvir/ledipasvir in genotype 1, sofosbuvir and ribavirin in genotype 2, and sofosbuvir/velpatasvir in genotypes 3 to 6. The incremental analysis shown in Table 16 shows GP dominating the comparator portfolio, i.e., it has higher quality-adjusted life-years (QALYs) (0.084 additional QALYs for GP) and lower costs ($12,473 less for GP).[3]

Table 16: Manufacturer's Base Case: Incremental Analysis in the Portfolio Approach

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR ($/QALY)
Comparator portfolio	68,360	19.41			
Glecaprevir/pibrentasvir	55,887	19.50	−12,473	0.084	Dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: manufacturer's pharmacoeconomic submission.[3]

Base Case: Segmented Approach

In segment analysis, the manufacturer compared GP with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r/DSV), elbasvir/grazoprevir, sofosbuvir/velpatasvir, and sofosbuvir/ledipasvir, as well as with no treatment in different patient segments (according to genotype, treatment experience, and presence or absence of cirrhosis). In genotype 1 patients with fibrosis stages 0 to 3, GP was a dominant strategy compared with the other all-oral DAA. Compared with the no-treatment option, GP has an incremental cost-utility ratio (ICUR) of $2,319 per QALY (Table 17).

Table 17: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 1

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
Genotype 1 treatment-naive patients (F3 to F0)						
No treatment	42,101	16.707				
GP	49,253	19.964	7,152	3.257	2,319	2,319
SOF/LDV	55,839	19.821	13,738	3.114	4,412	Dominated
OBV/PTV/r/DSV	66,240	19.893	24,139	3.186	7,577	Dominated
SOF/VEL	69,841	19.946	27,740	3.239	8,564	Dominated
EBR/GZR	72,012	19.758	29,911	3.051	9,804	Dominated
Genotype 1 treatment-naive patients (F4)						
No treatment	75,561	11.635				
OBV/PTV/r/DSV	92,062	16.184	16,501	4.549	3,627	3,627
GP	93,715	16.470	18,154	4.835	3,755	5,780
SOF/VEL	94,075	16.404	18,514	4.769	3,882	Dominated
EBR/GZR	95,710	16.251	20,149	4.616	4,365	Dominated
SOF/LDV	102,558	16.182	26,997	4.547	5,937	Dominated
Genotype 1 patients previously treated with PRS (F0 to F3)						
No treatment	45,176	16.263				
GP	50,357	19.735	5,181	3.472	1,492	1,492
OBV/PTV/r/DSV	67,048	19.647	21,872	3.384	6,463	Dominated

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
SOF/VEL	70,616	19.710	25,440	3.447	7,380	Dominated
EBR/GZR	72,672	19.508	27,496	3.245	8,473	Dominated
SOF/LDV	78,764	19.600	33,588	3.337	10,065	Dominated
Genotype 1 patients previously treated with PRS (F4)						
No treatment	75,034	11.575				
SOF/VEL	93,712	16.270	18,678	4.695	3,978	3,978
GP	95,173	16.128	20,139	4.553	4,423	Dominated
EBR/GZR	96,327	15.977	21,293	4.402	4,837	Dominated
OBV/PTV/r/DSV	111,848	16.131	36,814	4.556	8,080	Dominated
SOF/LDV	166,102	16.331	91,068	4.756	19,148	1,186,721

EBR/GZR = elbasvir/grazoprevir; F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; OBV/PTV/r/DSV = ombitasvir/paritaprevir/ritonavir/dasabuvir; PRS = pegylated interferon + ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF/LDV = sofosbuvir/ledipasvir; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission.[3]

In genotype 1 patients previously treated with an NS5A inhibitor, the "no treatment" option had lower costs and lower QALYs than GP. As such, GP had an incremental ICUR of $13,097 per QALY when compared with the no-treatment option (Table 18).

Table 18: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 1 Patients Previously Treated with an NS5A Inhibitor

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR ($/QALY)
No treatment	50,493	15.43			
GP	96,440	18.94	45,947	3.51	13,097

GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[3]

In genotype 1 patients previously treated with an NS3/4A inhibitor, the "no treatment" option had lower costs and QALYs than GP, therefore resulting in an ICUR of $6,383 per QALY when compared with the no-treatment option. When compared against elbasvir/grazoprevir, GP dominated elbasvir/grazoprevir (resulted in additional benefits at lower costs) in genotype 1 patients previously treated with an NS3/4A inhibitor (Table 19).

Table 19: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 1 Patients Previously Treated With an NS3/4A Inhibitor

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
No treatment	50,493	15.43				
GP	74,272	19.15	23,779	3.72	6,383	6,383
EBR/GZR	76,422	19.01	25,929	3.58	7,242	Dominated

EBR/GZR = elbasvir/grazoprevir; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: manufacturer's pharmacoeconomic submission[3]

Table 20: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 2

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
Genotype 2 treatment-naive patients (F3 to F0)						
No treatment	34,355	17.653				
GP	48,509	20.056	14,154	2.403	5,891	5,891
SOF + RBV	64,036	19.990	29,681	2.337	12,701	Dominated
SOF/VEL	68,382	20.061	34,027	2.408	14,131	3,974,600
Genotype 2 treatment-naive patients (F4)						
No treatment	78,178	12.302				
SOF + RBV	93,089	16.103	14,911	3.801	3,923	Extendedly dominated
SOF/VEL	93,555	16.547	15,377	4.245	3,622	3,622
GP	93,933	16.547	15,755	4.245	3,711	Dominated
Genotype 2 patients previously treated with PRS (F0 to F3)						
No treatment	37,446	17.283				
GP	51,367	19.635	13,921	2.352	5,919	5,919
SOF + RBV	67,514	19.554	30,068	2.271	13,240	Dominated
SOF/VEL	68,808	19.861	31,362	2.578	12,165	77,173
Genotype 2 patients previously treated with PRS (F4)						
No treatment	77,595	12.233				
SOF/VEL	93,187	16.410	15,592	4.177	3,733	3,733
GP	93,565	16.410	15,970	4.177	3,823	Dominated
SOF + RBV	98,657	15.452	21,062	3.219	6,543	Dominated

F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = pegylated interferon + ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF + RBV = sofosbuvir and ribavirin; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission.[3]

Table 21: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 3

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
Genotype 3 treatment-naive patients (F3 to F0)						
No treatment	46,737	15.801				
GP	52,116	19.697	5,379	3.896	1,380	1,380
SOF/VEL	70,599	19.832	23,872	4.031	5,922	102,348
SOF + RBV	120,636	19.532	73,909	3.731	19,809	Dominated
Genotype 3 treatment-naive patients (F4)						
No treatment	72,828	10.945				
GP	93,948	16.304	21,120	5.359	3,941	3,941
SOF/VEL	95,877	16.010	23,049	5.065	4,551	Dominated
SOF + RBV	149,585	15.141	76,757	4.196	18,293	Dominated
Genotype 3 patients previously treated with PRS (F0 to F3)						
No treatment	49,415	15.321				
SOF/VEL	74,060	19.286	24,246	3.965	6,216	6,216

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost ($/QALY)	Sequential ICUR ($/QALY)
GP	92,768	19.473	43,353	4.152	10,442	99,877
SOF + RBV	125,331	18.845	75,916	3.524	21,543	Dominated
Genotype 3 patients previously treated with PRS (F4)						
No treatment	72,357	10.893				
SOF/VEL	97,026	15.676	24,669	4.783	5,158	5,158
GP	115,435	15.942	43,078	5.049	8,532	69,314
SOF+R	156,512	14.032	84,155	3.139	26,810	Dominated

F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = pegylated interferon + ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF + RBV = sofosbuvir and ribavirin; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission.[3]

Table 22: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 4

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost	Sequential ICUR ($/QALY)
Genotype 4 treatment-naive patients (F3 to F0)						
No treatment	40,821	16.863				
GP	51,380	19.769	10,558	2.906	3,633	3,633
SOF/VEL	69,148	20.012	28,327	3.149	8,996	77,878
EBR/GZR	69,486	20.008	28,665	3.145	9,115	Dominated
Genotype 4 treatment-naive patients (F4)						
No treatment	75,825	11.702				
SOF/VEL	93,521	16.478	17,696	4.776	3,705	3,705
GP	93,737	16.478	17,912	4.776	3,751	Dominated
EBR/GZR	93,859	16.474	18,034	4.772	3,779	Dominated
Genotype 4 patients previously treated with PRS (F0 to F3)						
No treatment	43,941	16.426				
GP	49,683	19.779	5,742	3.353	1,713	1,713
SOF/VEL	69,884	19.780	25,943	3.354	7,735	10,978,774
EBR/GZR	89,840	19.776	45,899	3.350	13,702	Dominated
Genotype 4 patients previously treated with PRS (F4)						
No treatment	75,292	11.641				
SOF/VEL	93,160	16.343	17,868	4.702	3,800	3,800
GP	93,376	16.343	18,083	4.702	3,846	Dominated
EBR/GZR	113,117	16.339	37,825	4.698	8,051	Dominated

EBR/GZR = elbasvir/grazoprevir; F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = pegylated interferon + ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission.[3]

Table 23: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 5

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost	Sequential ICUR ($/QALY)
Genotype 5 treatment-naive patients (F3 to F0)						
No treatment	40,821	16.863				
GP	48,948	20.011	8,127	3.148	2,582	2,582
SOF/VEL	70,239	19.904	29,418	3.041	9,674	Dominated
Genotype 5 treatment-naive patients (F4)						
No treatment	75,825	11.702				
SOF/VEL	93,521	16.478	17,696	4.776	3,705	3,705
GP	93,737	16.478	17,912	4.776	3,751	Dominated
Genotype 5 patients previously treated with PRS (F0 to F3)						
No treatment	43,941	16.426				
GP	49,683	19.779	5,742	3.353	1,713	1,713
SOF/VEL	69,884	19.780	25,943	3.354	7,735	10,978,774
Genotype 5 patients previously treated with PRS (F4)						
No treatment	75,292	11.641				
SOF/VEL	93,160	16.343	17,868	4.702	3,800	3,800
GP	93,376	16.343	18,084	4.702	3,846	Dominated

F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = pegylated interferon + ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission[3]

Table 24: Manufacturer's Base Case: Incremental Analysis in the Segmented Approach for Genotype 6

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost	Sequential ICUR ($/QALY)
Genotype 6 treatment-naive patients (F3 to F0)						
No treatment	40,821	16.863				
GP	52,899	19.617	12,078	2.754	6,066	4,385
SOF/VEL	69,148	20.012	28,327	3.149	8,996	29,423
Genotype 6 treatment-naive patients (F4)						
No treatment	75,825	11.702				
SOF/VEL	93,521	16.478	24,912	4.776	3,705	3,705
GP	93,737	16.478	17,912	4.776	3,751	Dominated

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR Versus Lowest Cost	Sequential ICUR ($/QALY)
Genotype 6 patients previously treated with PRS (F0 to F3)						
No treatment	43,941	16.426				
GP	49,683	19.779	5,442	3.353	1,713	1,713
SOF/VEL	69,883	19.780	25,943	3.354	7,735	10,978,774
Genotype 6 patients previously treated with PRS (F4)						
No treatment	75,292	11.641				
SOF/VEL	93,160	16.343	17,868	4.702	3,800	3,800
GP	93,376	16.343	18,084	4.702	3,846	Dominated

F0–F4 = METAVIR fibrosis stages; GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; PRS = peginterferon/ribavirin + sofosbuvir; QALY = quality-adjusted life-year; SOF/VEL = sofosbuvir/velpatasvir.
Source: Manufacturer's pharmacoeconomic submission.[3]

Manufacturer's Results: Secondary Analyses

The manufacturer's attempts to conduct secondary analyses in subpopulations with unmet medical needs were unsuccessful for patients who have failed a DAA-containing regimen (no approved treatments for this subpopulation of HCV patients) and patients infected with HCV genotype 2, 3, 5, or 6 who have chronic kidney disease (CKD) as currently there are no interferon- or ribavirin-free regimens suitable for use in patients infected with genotype 2, 3, or 5, and patients with genotype 6 with CKD stage 4 and 5. However, in genotype 3 treatment-experienced patients with cirrhosis, GP resulted in an ICUR of $69,314 per QALY when compared with sofosbuvir/velpatasvir.

Deterministic one-way sensitivity analyses revealed that the results are sensitive to SVR rates in both cirrhotic and non-cirrhotic patients for both GP and the comparators.

Different scenario analyses were conducted by the manufacturer in the base case using the portfolio approach: varying the baseline patient characteristics and the discounting rate, considering a societal perspective, and assessing the impact of the inclusion of the costs associated with ribavirin, based on the average patient weight reported in the GP phase III clinical trials. As reported by the manufacturer, GP remained the dominant option in the treatment of HCV genotype 1 to 6 patients compared with other available and reimbursed HCV therapies across the scenarios considered.

As a reminder, the manufacturer did not report on the deterministic sensitivity analyses on the segmented approach.

Finally, the manufacturer considered a scenario analysis using the portfolio approach where a societal perspective was adopted by including indirect costs associated with productivity loss. Despite the limitations with the manufacturer's portfolio approach, the scenario analysis illustrates that applying a broader perspective would maintain the dominance of GP over the comparator portfolio (Table 25).

Table 25: Manufacturer's Scenario Case: Incremental Analysis in the Portfolio Approach Using the Societal Perspective

Outcome	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR ($/QALY)
Comparator portfolio	85,043	19.41			
GP	70,148	19.50	−14,895	0.084	Dominant

GP = glecaprevir/pibrentasvir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: manufacturer's pharmacoeconomic submission.[3]

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