Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	eltrombopag (Revolade) 25 mg and 50 mg tablets
Indication	To increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy.
Listing request	To increase platelet counts in thrombocytopenic patients with chronic HCV infection due to genotype 2 or 3 to allow the initiation and maintenance of interferon-based therapy.
Manufacturer	GlaxoSmithKline Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in hepatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
AVT	antiviral therapy
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
DC	decompensated cirrhosis
ELT	eltrombopag
EVR	early virologic response
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
PEG-IFN	pegylated interferon
PEG-IFN-α	pegylated interferon alfa
QALY	quality-adjusted life-year
SVR	sustained virologic response
TCP	thrombocytopenia
TEE	thromboembolic events
TTO	time trade-off

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Eltrombopag (Revolade)
Study Question	"The primary objective for this evaluation was whether treatment with [ELT] to enable initiation of PEG-IFN-α–based AVT and subsequent treatment with [ELT] alongside PEG-IFN-α–based AVT is cost-effective for the treatment of TCP in patients with chronic HCV compared with the current standard of care for these patients (no enabling TCP treatment and a reduced dose of PEG-IFN–based AVT)."
Type of Economic Evaluation	CUA
Target Population	Adult patients with chronic HCV who had a platelet count precluding AVT (baseline platelet count of < 75,000/μL — as per ENABLE 1 and ENABLE 2 studies)
Treatment	ELT once daily as an enabling treatment and subsequent treatment alongside AVT (interferon-based therapy) Starting dose: 25 mg Dose escalation to 50 mg, 75 mg, and 100 mg as required to achieve treatment threshold platelet count
Outcomes	QALYs, life-years, costs, % of EVR patients, % of SVR patients, % of DC, % of HCC events, liver transplants avoided, deaths
Comparators	**Strategy I:** Enabling treatment with ELT and subsequent ELT treatment alongside AVT (as in ENABLE trials) **Strategy II:** No enabling treatment with ELT and a reduced dose of PEG-IFN (when platelets are in the 25,000/μL to 50,000/μL and 50,000/μL to 90,000/μL ranges), and no PEG-IFN treatment for patients with platelets < 25,000/μL
Perspective	Canadian Provincial Ministry of Health
Time Horizon	Lifetime (50 years)
Results for Base Case	$106,926 per QALY for all patients $55,446 per QALY for the subgroup of genotype 2 or 3 patients
Key Limitations	• There is uncertainty around platelet count thresholds required for AVT initiation, which results in increased uncertainty regarding the economic evaluation and may have biased the efficacy results in favour of ELT. • For the comparator-reduced-dose AVT regimen, larger dose reductions than what have been recommended and used in clinical practice have been assumed, which bias the results in favour of ELT. • The source for the efficacy of the comparator-reduced-dose AVT is inappropriate; therefore, the estimate is highly uncertain. • Considering the baseline average patient age is 51 years and the uncertainty around many parameters, the time horizon of 50 years may be too long. • CDR did not consider the data sources for long-term costs and natural history of disease to be the most appropriate available.
CDR Estimates	$166,040 per QALY for all patients $90,060 per QALY for the subgroup of genotype 2 or 3 patients

AVT = antiviral therapy; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DC = decompensated cirrhosis; ELT = eltrombopag; EVR = early virologic response; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; PEG-IFN-α = pegylated interferon alfa; QALY = quality-adjusted life-year; SVR = sustained virologic response; TCP = thrombocytopenia.

EXECUTIVE SUMMARY

Background

Eltrombopag (Revolade) is being reviewed as an enabling and subsequent treatment alongside antiviral therapy (AVT) to increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy. It is available as 25 mg and 50 mg oral tablets and the recommended dose is 25 mg to 100 mg once daily, adjusted as necessary, to achieve the target platelet count to initiate or maintain AVT, or a daily cost ranging from $62.50 to $250.

The manufacturer submitted a cost-utility analysis (CUA) over a patient lifetime horizon of 50 years, conducted from a Canadian public payer perspective.[1] The primary comparison was between eltrombopag enabling treatment and subsequent maintenance treatment alongside AVT (pegylated-interferon–based regimen) versus no enabling treatment and a reduced dose of pegylated interferon (when platelets are in 25,000/µL to 90,000/µL ranges) and no pegylated interferon (PEG-IFN) treatment for patients with platelets < 25,000/µL.

Summary of Identified Limitations and Key Results

The following main limitations with the manufacturer's economic model were identified:

Uncertainty Regarding Platelet Count Thresholds Required for AVT Initiation

In the economic model, patients were required to have platelet levels of 90,000/µL to 100,000/µL in order to start AVT, reflecting ENABLE studies. Although these thresholds are in line with the Canadian product monographs for PEG-IFN-alfa-2a and -2b, they may not accurately represent current Canadian clinical practice of more aggressive treatment and initiating AVT for lower platelet counts. This assumption could not be accounted for by CADTH Common Drug Review (CDR) and may bias the clinical efficacy in favour of eltrombopag.

Dose Reduction of Antiviral Therapy Regimen

For reduced-dose AVT regimen, the manufacturer assumed larger dose reductions than what has been recommended and used in clinical practice, which bias the results in favour of eltrombopag. CDR conducted reanalysis of the submitted model by using dose reductions in line with the Canadian guidelines.

Uncertainty Around Efficacy of Reduced-Dose Antiviral Therapy

The manufacturer based the efficacy estimate for reduced-dose AVT on an unpublished burden of illness study in Quebec, in which "reduced dose" treatment refers to reduced duration of treatment, rather than reduced dose. This estimate is not appropriate to inform the economic model.

Revised Long-Term Costs

The long-term chronic HCV costs were based on a study conducted in 2005.[2] There is a more recent Canadian longitudinal cohort study examining the costs associated with chronic HCV[3] that has been used for the *CADTH Therapeutic Review of Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*,[4] which was used in a revised base case.

Revised Natural History of Disease Data

The manufacturer identified several parameters estimating the natural disease progression as having a great impact on the cost-effectiveness results. The main data source for the natural progression of the disease was the HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis) study,[5] supplemented with published literature.[5-9] For the *CADTH Therapeutic Review of Direct-Aging Antiviral Agents for Chronic Hepatitis C Genotype 1*, data on disease progression were obtained from a systematic review conducted by Thein et al.,[7] which was used in a revised base case.

Revised Time Horizon

The economic model uses a lifetime horizon of 50 years. Considering the average baseline age of patients is 51 years and the uncertainty around many parameters (e.g., no immediate benefits with eltrombopag, benefits are gained over a long time horizon), CDR considered a 30-year time horizon to be more appropriate for reanalysis.

Duration of Antiviral Therapy

The model assumed that patients with genotype 2 or 3 were treated for 24 weeks and patients with HCV non-genotype 2 or 3 were treated for 48 weeks. As per the Canadian guidelines, previously untreated patients with genotype 2 or 3 would generally receive 24 weeks of AVT; however, if they do not have a rapid virologic response at four weeks and have other predictors of poor response, they may benefit from 36 weeks to 48 weeks of AVT. Longer AVT treatment duration beyond what was assumed in the base case will lead to higher incremental cost-utility ratios (ICURs).

Conclusions

When addressing the limitations to the submitted model mentioned above, CDR estimated the ICUR of enabling and maintenance treatment with eltrombopag versus reduced dose of AVT for the treatment of thrombocytopenia (TCP) to be $166,040 per quality-adjusted life-year (QALY) for all patients and $90,060 for patients who are genotype 2 or 3.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) comparing the use of eltrombopag with pegylated interferon alfa (PEG-IFN-alpha) (as part of an antiviral therapy [AVT] strategy) compared with AVT alone, over a patient lifetime horizon of 50 years, conducted from a Canadian public payer perspective. The model consisted of three phases: enabling phase, maintenance phase, and long-term sustained virologic response (SVR) phase. The first two phases mirror the ENABLE 1 and ENABLE 2 clinical studies[10-12] and were modelled as a decision tree. The last phase was constructed as a Markov model in which costs and outcomes were extrapolated over a long-term period, simulating disease progression. The primary comparison was between eltrombopag enabling treatment and subsequent maintenance treatment alongside AVT versus no enabling treatment and a reduced dose of pegylated interferon (PEG-IFN) (when platelets are in 25,000/µL to 90,000/µL ranges) and no PEG-IFN treatment for patients with platelets < 25,000/µL.

The efficacy of the eltrombopag treatment in the enabling and maintenance phases is based on pooled patient level dataset from the initiation pre-AVT phase of the ENABLE studies.[10-12] For patients receiving reduced-dose AVT, the clinical efficacy in terms of SVR is derived from the ENABLE placebo group, adjusted with relative risk of achieving SVR versus full-dose AVT from the unpublished burden of illness study of patients with chronic HCV in Quebec (Appendix C, Manufacturer's Pharmacoeconomic submission).[1] In the long-term SVR phase of the model, patients progress through the fibrosis steps (F0, F1/2, F3, F4) based on natural history progression and SVR status. Data on natural history of disease are based on published literature.[5,6,8,9] The utility weights for the enabling and maintenance phases are based on data collected in the ENABLE studies, mapped to SF-6D. For the long-term SVR phase of the model, the utilities are based on published literature.[13] The model incorporates the dose regimens and treatment duration as per the ENABLE clinical trials.

2. MANUFACTURER'S BASE CASE

In the manufacturer's base case, the incremental cost and quality-adjusted life-years (QALYs) of eltrombopag enabling and maintenance treatment alongside full-dose AVT versus no enabling treatment followed by reduced-dose AVT for all patients are $36,562 and 0.34 QALYs, leading to an incremental cost per QALY of $106,926. In the genotype 2 or 3 patient population, the incremental cost and QALYs of eltrombopag enabling and maintenance treatment alongside full-dose AVT versus no enabling treatment followed by reduced-dose AVT for all patients is $27,126 and 0.49 QALYs, leading to an incremental cost per QALY of $55,446.

2.1 Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses that varied model parameters by using alternative values.

2.1.1 One-Way Sensitivity Analyses

The following parameters increased the incremental cost per QALY gained by more than 25% for eltrombopag:

- Shortening the time horizon to 10 years resulted in cost per QALY of $399,992 for all patients and $205,879 for genotype 2 or 3 patients.
- Using the time trade-off (TTO) utility values resulted in cost per QALY of $73,306 for all patients and $37,667 for genotype 2 or 3 patients.
- Decreasing the transitional probability for patients with no SVR from F4 to hepatocellular carcinoma (HCC) to 0.0224 resulted in cost per QALY of $59,442 for all patients and $33,347 for genotype 2 or 3 patients.
- Increasing the transitional probability for patients with no SVR from F4 to HCC to 0.1304 resulted in cost per QALY of $201,764 for all patients and $89,245 for genotype 2 or 3 patients.
- Increasing relative risk of SVR for reduced-dose AVT (upper 95% confidence limit) resulted in cost per QALY of $148,557 for all patients and $94,885 for genotype 2 or 3 patients.
- Increasing relative risk of SVR for reduced-dose AVT (upper 95% confidence limit) resulted in cost per QALY of $89,565 for all patients and $42,170 for genotype 2 or 3 patients.

2.1.2 Probabilistic Sensitivity Analysis

Based on the probabilistic sensitivity analyses, there is a 41% likelihood for all patients and 82% likelihood for genotype 2 or 3 patients that the incremental cost per QALY for eltrombopag would fall below $50,000.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Uncertainty Regarding Platelet Count Thresholds Required for Antiviral Therapy Initiation

Patients in the ENABLE studies were required to have platelet levels of 90,000/µL (ENABLE 1) or 100,000/µL (ENABLE 2) in order to start AVT. These thresholds have been applied in the economic model. Although Canadian product monographs for PEG-IFN-alfa-2a and -2b advise caution when starting AVT in patients with platelet counts less than 90,000 µL to 100,000 µL and recommend PEG-IFN dosage reduction and discontinuation if platelets fall below 50,000 µL and 25,000/µL respectively, based on the most recent update of Canadian guidelines for management of chronic HCV,[14] these limits have been challenged by experts who suggest that PEG-IFN dose reductions are not necessary until the platelet count falls below 30,000/µL, with discontinuation if the platelets fall below 20,000/µL. According to the clinical expert, many experienced Canadian physicians treat more aggressively and initiate and maintain AVT in much lower platelet counts than was done in the trials; therefore, the ENABLE studies may not accurately represent current clinical practice in Canada, which increases uncertainty with the economic evaluation. In addition, this may have biased the efficacy results in favour of eltrombopag because AVT was likely stopped sooner in the placebo groups than is currently done in clinical practice.

3.2 Dose Reduction of Antiviral Therapy Regimen

For the main comparator — reduced-dose AVT regimen — the manufacturer assumed that patients with platelet counts of less than < 25,000/µL will not be treated with AVT, patients with platelet counts between 25,000/µL and 50,000/µL will be treated with a dose reduction of 50% of the recommended PEG-IFN dose, and patients with platelet counts higher than 50,000/µL will be treated with a dose reduction of 75% of the recommended dose. Based on the guidelines, the minimum effective dose of PEG-IFN

appears to be 1 mcg/kg/week (66.7% reduction of the full dose),[14] as opposed to 50% dose reduction applied in the economic model. The CADTH Common Drug Review (CDR) conducted reanalysis of the submitted model by using dose reductions in line with the Canadian guidelines, i.e., 66.7% reduction for patients with platelet counts between 25,000/µL and 50,000/µL, and no dose reduction for patients with platelet counts more than 50,000/µL.

3.3 Uncertainty Regarding Efficacy of Reduced-Dose Antiviral Therapy

The model utilizes relative risk of [redacted] of achieving SVR after reduced-dose AVT compared with full-dose AVT, based on an unpublished burden of illness study in Quebec. The study is a retrospective chart review study on a total of 175 patients with chronic HCV, and 70 patients with thrombocytopenia (TCP). CDR Clinical Reviewers (CDR Clinical Report, Appendix 6) critically appraised the analysis, and it was found that the "reduced dose" treatment in the analysis refers to reduced duration of treatment, rather than reduced dose. Therefore, the results are not appropriate to inform the economic model. The width of the 95% confidence intervals (CIs) ([redacted]-[redacted]) confirms the uncertainty regarding this parameter. As an alternative to the base-case estimate, the relative efficacy of reduced-dose AVT versus full-dose AVT was estimated using large randomized controlled trial Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C).[5] Although this study included only patients with genotype 1, due to the validity of the study, CDR deemed this source to be more appropriate to inform the efficacy of reduced-dose AVT. Using the dose reduction magnitude as per the previous limitation and using HALT-C study as a source, CDR estimated the average RR of SVR for reduced-dose AVT versus full-dose AVT to be 0.79, which resulted in an ICUR of $122,414 for all patients and $70,219 for patients with genotype 2 or 3.

3.4 Revised Long-Term Costs

The long-term chronic HCV costs were based on a study by El Saadany (2005).[2] There is a newer Canadian longitudinal cohort study by Krajden et al. (2010),[3] examining the costs associated with chronic HCV, that has been used for the *CADTH Therapeutic Review of Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1* recently conducted.[4] This study resulted with significantly higher costs related to chronic HCV than the study used in the submitted model. CDR conducted reanalysis using the costs as reported in this study, resulting with an ICUR of $113,951 for all patients and $62,443 for patients with genotype 2 or 3 patients.

3.5 Revised Natural History of Disease Data

Several parameters estimating the natural disease progression were identified by the manufacturer to have great impact to the cost-effectiveness results. The main data source for the natural progression of the disease was HALT-C study,[5] supplemented with published literature where unavailable.[5,6,8,9] For the *CADTH Therapeutic Review of Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*, data on disease progression were obtained from a systematic review conducted by Thein et al. (2008).[7] CDR conducted a reanalysis based on this source for natural history of disease data, which resulted in an ICUR of $57,885 for patients with genotype 2 or 3 and $119,886 for all patient populations.

3.6 Revised Time Horizon

The economic model uses a lifetime horizon of 50 years. Considering the average baseline age of patients is 51 years and the uncertainty around many parameters (e.g., no immediate benefits with eltrombopag, benefits are gained over a long time horizon), CDR considered a 30-year time horizon to be more appropriate for reanalysis, resulting in an ICUR of $57,885 for patients with genotype 2 or 3 and $119,886 for all patient populations.

3.7 Duration of Antiviral Therapy

The manufacturer assumed that patients with HCV genotype 2 or 3 were treated for 24 weeks and patients with HCV non-genotype 2 or 3 were treated for 48 weeks. Based on Canadian guidelines, previously untreated patients with genotype 2 or 3 would generally receive 24 weeks of AVT; however, if they do not have a rapid virologic response at 4 weeks and have other predictors of poor response, they may benefit from 36 weeks to 48 weeks of AVT. Longer AVT treatment duration beyond what was assumed in the base case will lead to higher ICURs.

4. CADTH COMMON DRUG REVIEW ANALYSES

When accounting for the limitations listed above, CDR considered a best estimate of the cost-effectiveness of eltrombopag based on the following (not accounting for platelet count thresholds required for AVT initiation):

- Revised AVT dose reductions
- Revised efficacy for reduced-dose AVT
- Revised chronic HCV costs
- Revised natural history of disease inputs
- Revised time horizon (30 years)

The results of the CDR estimate are outlined in Table 2.

TABLE 2: CADTH COMMON DRUG REVIEW REANALYSIS BEST ESTIMATE

ELT Enabling and Maintenance Therapy Versus Reduced-Dose AVT	Difference in QALYs	Difference in Life-Years	Difference in Costs	CDR Best Estimate ICUR
Genotype 2 or 3 patients	0.3384	0.55	$30,478	$90,060
All patients	0.225	0.37	$37,351	$166,040

AVT = antiviral therapy; CDR = CADTH Common Drug Review; ELT = eltrombopag; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

4.1 CADTH Common Drug Review Price Reduction Scenarios

Based on the revised best estimate, a 50% price reduction under this scenario would result in ICURs of less than $50,000 for patients who are genotype 2 and 3, or less than $100,000 for all patients (Table 14).

5. PATIENT INPUT

- Patient groups indicated that eltrombopag has serious side effects and that the patients need to be carefully prepared and monitored during treatment; however, patients are willing to endure fairly severe side effects if they can be cured. The economic model included only thromboembolic events (TEE) and cataract surgery as adverse events.
- One of the patient groups reported that patients with chronic HCV with low platelets are currently given infusions, injections, and — less frequently — transfusions, which are both painful and inconvenient. These have not been included in the submitted economic model.

6. CONCLUSION

CDR identified several limitations with the data estimates and assumptions used in the manufacturer's submitted model. When addressing the identified limitations, the ICUR of enabling and maintenance treatment with eltrombopag versus reduced dose of AVT for the treatment of TCP increased to $166,040 per QALY for all patients and $90,060 for the genotype 2 or 3 patient population.

APPENDIX 1: COST COMPARISON

The comparators presented in the table below 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.

TABLE 3: COST COMPARISON TABLE FOR ELTROMBOPAG

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Eltrombopag (Revolade)[a]	25 mg 50 mg	Tablet	62.50 125.00	25 mg daily (max. 100 mg)	62.50 (max. 250.00)	22,812.50 (max. 92,250.00)

max. = maximum.
[a] Manufacturer-submitted price.

No comparators were identified for the specific indication of "to increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy."[15]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ELTROMBOPAG RELATIVE TO THE REDUCED-DOSE ANTIVIRAL THERAPY?

Eltrombopag vs. Reduced-Dose AVT	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					x	
Drug treatment costs alone					x	
Clinical outcomes	x					
QoL			x			
Incremental CE ratio or net benefit calculation[a]	**$90,060 per QALY for genotype 2 or 3 patient population $166,040 per QALY for all patient populations**					

AVT = antiviral therapy; CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; QoL = quality of life; vs. = versus.
[a] As per CDR reviewer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	x		
Was the material included (content) sufficient?	x		
Was the submission well organized and was information easy to locate?	x		

TABLE 6: AUTHOR INFORMATION

Authors	Affiliations
Isobel Pearson	RTI Health Solutions

	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 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis (CUA) in the form of a decision tree/Markov model over a lifetime horizon of 50 years, conducted from a public payer perspective.[1] The model consisted of three phases: enabling phase, maintenance phase, and long-term sustained virologic response (SVR) phase. The first two phases mirror the ENABLE 1 and ENABLE 2 clinical studies[10-12] and are being modelled as a decision tree. The last phase of the model is a Markov model in which costs and outcomes are extrapolated over a long-term period, simulating disease progression.

The model included four alternative treatment strategies:

Strategy 1: Enabling treatment with eltrombopag and subsequent eltrombopag treatment alongside AVT (as in the ENABLE studies).

Strategy 2: Enabling treatment with eltrombopag and subsequent antiviral therapy (AVT) without eltrombopag treatment (as in the ENABLE studies).

Strategy 3: No enabling treatment with eltrombopag and no AVT (current management in strict accordance with pegylated interferon [PEG-IFN] label detailing sufficient platelet levels to initiate therapy; ≥ 90,000/µL for PEG-IFN-α-2a and ≥ 100,000/µL for PEG-IFN-α-2b).

Strategy 4: No enabling treatment with eltrombopag and a reduced dose of PEG-IFN (reduced AVT doses observed when platelets are in the 25,000/µL to 90,000/µL ranges), and no PEG-IFN treatment for patients with platelets < 25,000/µL.

The primary comparison of the submitted economic evaluation is between strategy 1 and strategy 4, as it was deemed by the submitter to be most appropriate for clinical practice. The clinical expert engaged for this CADTH Common Drug Review (CDR) agreed that strategy 4 is the most appropriate comparator and found the other two strategies inapplicable. Therefore, the focus of CDR is only around the comparison of strategy 1 and strategy 4.

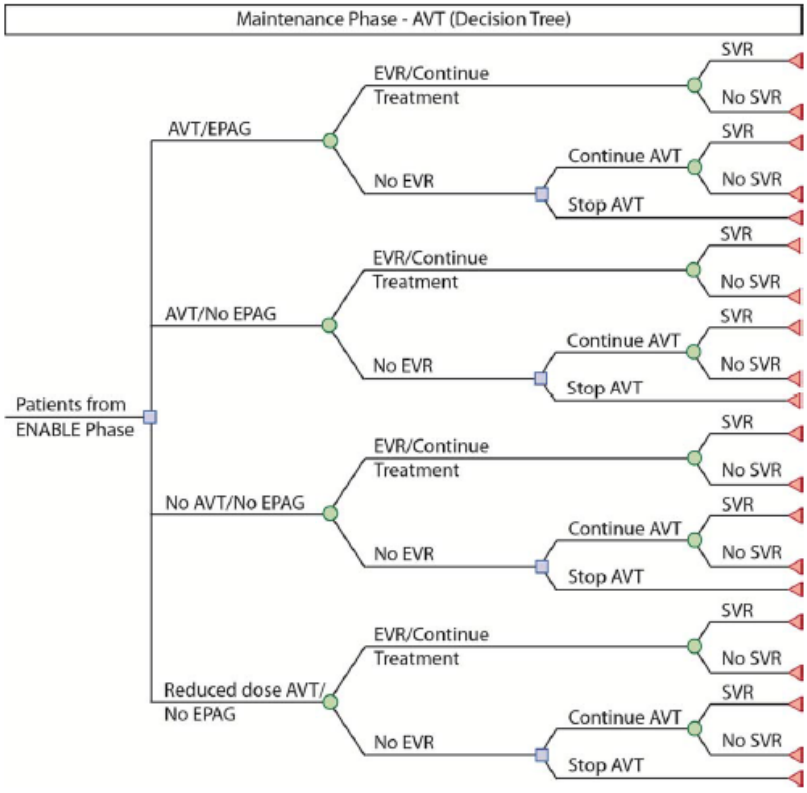
Patients with thrombocytopenia (TCP) enter the model in the enabling phase (Figure 1).

FIGURE 1: MODEL SCHEMATIC OF PHASE 1 (ENABLING PHASE) OF THE SUBMITTED MODEL

AVT = antiviral therapy; cHVC = chronic hepatitis C virus; DC = decompensated cirrhosis; EPAG = eltrombopag; F = fibrosis or cirrhosis score.
Source: Manufacturer's pharmacoeconomic (PE) submission.[1]

The patients on eltrombopag treatment are treated for up to nine weeks. Those patients who achieve target platelet levels start AVT treatment with maintenance eltrombopag, while patients who fail to achieve target platelet levels stop and exit the model. Patients who are not being treated with eltrombopag initiate with a reduced-dose AVT (Strategy 4), after which the patients enter the maintenance phase of the model (Figure 2).

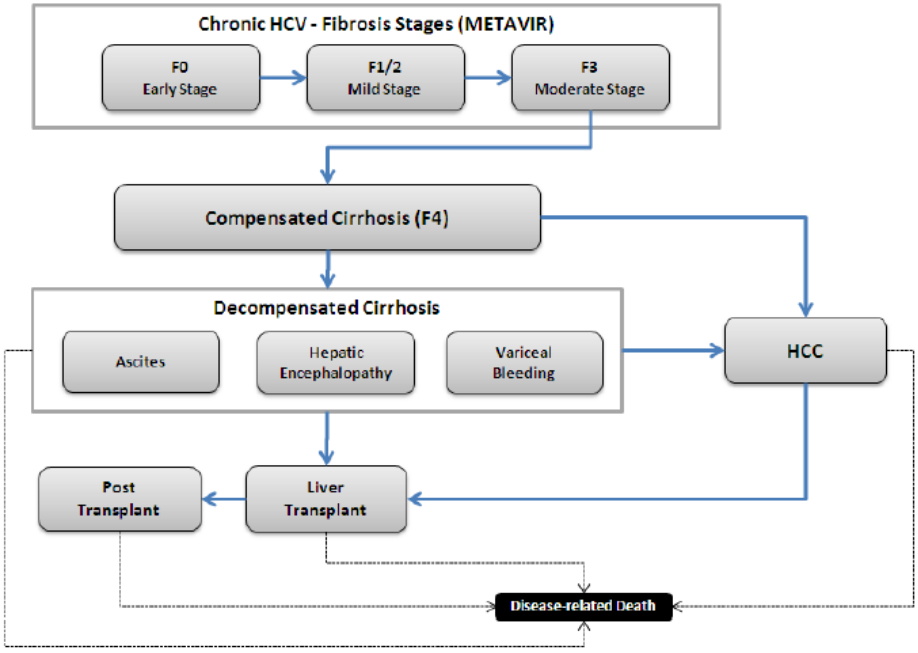
FIGURE 2: MODEL SCHEMATIC OF PHASE 2 (MAINTENANCE PHASE) OF THE SUBMITTED MODEL



AVT = antiviral therapy; EPAG = eltrombopag; EVR = early virologic response; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic (PE) submission.[1]

In the maintenance phase, patients receive treatment for up to 24 weeks (genotype 2 or 3 patients) or 48 weeks (non-genotype 2 or 3 patients). Patients are evaluated for early virologic response (EVR) at 12 weeks and for virologic response at 24 weeks and 48 weeks. Those achieving EVR continue treatment, whereas those not achieving EVR either continue treatment or stop treatment. Those achieving virologic response were evaluated for SVR after 24 weeks and enter the phase 3 of the model, the Markov model (Figure 3).

FIGURE 3: MODEL SCHEMATIC OF PHASE 3 (MARKOV MODEL) OF THE SUBMITTED MODEL



F = fibrosis or cirrhosis score; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; METAVIR = METAVIR fibrosis scoring system; SVR = sustained virologic response.
Source: Manufacturer's pharmacoeconomic submission.[1]

The health states in the Markov model (phase 3) are defined by METAVIR fibrosis scores (F0, F1/2, and F3), compensated cirrhosis (F4), states indicative of decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LTx), post-liver transplant (post-LTx), and death (Figure 3). Patients progress through the fibrosis steps based on natural history progression rates and SVR status.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	**Enabling phase:** Pooled patient level dataset from the open-label, initiation pre-AVT phase of ENABLE studies. **Maintenance phase:** Pooled patient level dataset from ENABLE studies for patients receiving ELT treatment. For patients receiving reduced-dose AVT, the clinical efficacy in terms of SVR was derived from the ENABLE placebo group adjusted with relative risk of achieving SVR vs. full-dose AVT from an unpublished burden of illness study of chronic HCV patients in Quebec. The EVR outcomes for the reduced-dose AVT	As per CDR clinical review, the efficacy findings may reflect a bias in favour of ELT, as AVT treatment in placebo patients may have been reduced or discontinued at higher platelet levels than is currently done in clinical practice due to the requirement for adherence to product labelling. In addition, the RR estimate of achieving SVR with reduced-dose vs. full-dose AVT is an important parameter in the model that has great impact on CE results. This input has been estimated from an unpublished burden of illness and refers to "reduced dose" with respect to those patients who did not complete a full course of treatment (i.e., reduced duration of treatment), and therefore it is inappropriate.

Data Input	Description of Data Source	Comment
	strategy were assumed to be equal to AVT without ELT strategy from ENABLE studies.	
Natural History	Long-term liver disease progression in patients not achieving SVR was based on data from HALT-C study, supplemented with Townsend et al.[8] and Wright et al.[6] studies, where unavailable. For patients achieving SVR, the hazard rations for disease progression for SVR compared with non-SVR were based on HALT-C study.	The same liver disease progression data were used for all patients and genotype 2 or 3 patients, which is likely appropriate. CADTH recently published *Therapeutic Review of Direct-acting Antiviral Agents for Chronic Hepatitis C Genotype 1*.[4] For the Therapeutic review, data on disease progression were obtained from a systematic review conducted by Thein et al. in 2008.[7] Although there is likely some uncertainty regarding the true transition rates, these rates were considered to be the most robust currently available in the literature and were acceptable by the clinical experts. CDR ran reanalysis using this natural progression of disease data.
Utilities	The utility weights for enabling and maintenance phase were based on SF-36 data collected in the ENABLE studies, mapped to SF-6D, and were applied at two levels of disease severity: patients remaining at F0 to F4 state during the study and patients transitioned to DC during the study. For the long-term SVR phase, the base-case model used utilities estimated using SF-6D data from the Hsu et al.[13] published study.	Utility-weight data were available at five specific points in the ENABLE trials: baseline, randomization, the 12-week assessment point on AVT, the end of AVT, and the final 24-week post-treatment assessment point of SVR. The model incorporated utility weights from different time points for the individual model strategies. For the enabling phase, ELT strategy utilities were calculated as an average utility weight across baseline and randomization assessment and for reduced-dose AVT as baseline utility weights. The utilities for the maintenance phase were calculated as an average across utilities at randomization assessment, 12-week assessment point on AVT, and end of AVT. It should be noted that the utility estimates for genotype 2 or 3 patients were lower than for the all patient population, suggesting worse quality of life for genotype 2 or 3 patients. There is no other available clinical data to confirm this difference.
Adverse events	The model included TEE and cataract surgery as AEs associated with ELT treatment.	
Mortality	All-cause mortality rates for the general population were obtained from Statistics Canada 2011. Disease progression mortality rates were obtained from natural history of disease published literature (HALT-C study[5] and Wright et al.[6]).	

Data Input	Description of Data Source	Comment
Costs		
Drug	The manufacturer provided the unit cost of ELT. The unit costs of AVT drugs were obtained from PMPRB, 2014. The ELT dose titration in the enabling phase has been obtained from the ENABLE studies. The final ELT dose required to achieve platelet response prior to AVT was used to calculate the cost of ELT in the enabling phase. The ELT and AVT average dose during the maintenance phase, as well as the treatment duration for both enabling and maintenance phases, was based on data from pooled ENABLE patient level data. It was assumed that duration of reduced-dose AVT is equal to the no-ELT group from the ENABLE studies. Reduced-dose AVT cost was assumed to be 60% of the AVT costs for the no-ELT group.	The model incorporates the dose regimens and treatment duration as per the ENABLE clinical trials. There are often large differences among dose regimen and treatment duration in the controlled clinical studies setting and real-world clinical practice that will further contribute to uncertainty around the CE estimate.
Monitoring	Cost of monitoring during treatment in terms of hematology and CBC tests were obtained from a published study by Brady et al.,[16] inflated to 2014 costs.	
Health state	The costs associated with long-term health states were based on a published Canadian study by El Saadany et al.[2]	

AE = adverse event; AVT = antiviral therapy; CBC = complete blood count; CDR = CADTH Common Drug Review; CE = cost-effectiveness; chronic HCV = chronic hepatitis C virus; DC = decompensated cirrhosis; ELT = eltrombopag; EVR = early virologic response; HALT-C = Hepatitis C Antiviral Long-term Treatment Against Cirrhosis; PMPRB = Patented Medicine Prices Review Board; RR = relative risk; SF-36 = Short Form (36) Health Survey; SVR = sustained virologic response; TEE = thromboembolic events; vs. = versus.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Patients with platelet counts of < 25,000/µL will not be treated with AVT; patients with platelet counts between 25,000/µL and 50,000/µL will be treated with a dose reduction of 50% of the recommended IFN dose; and patients with platelet counts greater than 50,000/µL will be treated with a dose reduction of 75% of the recommended dose.	According to the clinical expert, many experienced Canadian physicians treat more aggressively and initiate and maintain AVT in much lower platelet counts than was done in the trials; therefore, the ENABLE studies may not accurately represent current clinical practice in Canada. Also, as per Canadian guidelines,[14] the minimum effective dose of PEG-IFN appears to be 1 mcg/kg/week (66.7% reduction of the full dose), as opposed to 50% dose reduction applied in the economic model.
PEG-IFN-α-2a and PEG-IFN-α-2b could be considered to have equivalent efficacy as an AVT in treating chronic HCV.	Appropriate, based on the available clinical evidence.
Eltrombopag and AVT average doses during the maintenance phase, as well as the treatment duration for both enabling and maintenance phase were based on data from pooled ENABLE patient level data.	It is unlikely that drug utilization and treatment duration as seen in the clinical trials will be the same in real-world clinical settings.
Duration of reduced-dose AVT is equal to the placebo group from the ENABLE studies.	Likely inappropriate. AVT treatment in placebo patients may have been reduced or discontinued at higher platelet levels than is currently done in clinical practice due to the requirement for adherence to product labelling.
EVR outcomes for the reduced-dose AVT strategy were assumed to equal the EVR outcomes for the AVT without ELT strategy.	Uncertain.
The DC and HCC outcomes for the reduced-dose strategy 4 were assumed as equal to the annual proportion of patients transitioning from F4 to DC and HCC, respectively, for the progression of chronic HCV with no SVR.	Uncertain.
Genotype 2 or 3 patients will be on 24 weeks of AVT therapy, while patients with genotype 1 will be on 48 weeks of AVT therapy.	Per the Canadian guidelines, previously untreated patients with genotype 2 or 3 would generally receive 24 weeks of AVT; however, if they do not have a RVR at 4 weeks and have other predictors of poor prognosis they may benefit from 36 weeks to 48 weeks of AVT.

AVT = antiviral therapy; DC = decompensated cirrhosis; ELT = eltrombopag; EVR = early virologic response; F4 = cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; kg = kilogram; mcg = microgram; PEG-IFN = pegylated interferon; PEG-IFN-α-2a= pegylated interferon alfa-2a; PEG-IFN-α-2b= pegylated interferon alfa-2b; RVR = rapid virologic response; SVR = sustained virologic response; µL = microlitre.

Manufacturer's Results

All Patients

In the reference case, the incremental cost and QALYs of ELT enabling and maintenance treatment (strategy 1) versus reduced-dose AVT (strategy 4) for all patients are $36,562 and 0.34 QALYs, leading to an incremental cost per QALY of $106,926.

Genotype 2 or 3 Patients

In the genotype 2 or 3 patient population, the incremental cost and QALYs of ELT enabling and maintenance treatment (strategy 1) versus reduced-dose AVT (strategy 4) for all patients are $27,126 and 0.49 QALYs, leading to an incremental cost per QALY of $55,446.

TABLE 9: MANUFACTURER'S BASE-CASE RESULTS

	Total Costs ($)	Incremental Cost vs. Strategy 1 ($)	Total QALYs	Incremental QALYs vs. Strategy 1	ICUR ($) for Strategy 1 vs. Comparator
All patients					
ELT enabling and maintenance treatment	140,397		6.66		
Reduced-dose AVT	103,835	36,562	6.32	0.34	**106,926**
Genotype 2 or 3 patients					
ELT enabling and maintenance treatment	132,058		6.84		
Reduced-dose AVT	104,882	27,176	6.35	0.49	**55,446**

AVT = antiviral therapy; ELT = eltrombopag; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.

In addition, comparing eltrombopag enabling treatment and maintenance treatment alongside AVT (strategy 1) versus eltrombopag enabling only treatment with AVT maintenance (strategy 2) has been reported, which resulted in incremental $753,681 per QALY for all patients and $191,944 per QALY for genotype 2 or 3 patients.

One-Way Sensitivity Analyses

The following table is derived from the manufacturer's submission. It lists conducted one-way sensitivity analyses and their results that have significant impact on the results. The natural progression for non-SVR patients from F4 to HCC and the relative risk of SVR for reduced-dose AVT deemed to be the most important parameters that have a big impact on the ICURs. The utility values were also shown to have an impact on the final results.

TABLE 10: MANUFACTURER'S ONE-WAY SENSITIVITY ANALYSIS RESULTS FOR THE COMPARISON AMONG STRATEGY 1 AND STRATEGY 4

Scenario	ICUR for All Patients ($)	ICUR for Genotype 2 or 3 Patients ($)
Base-case scenario	106,926	55,446
Time horizon of 10 years	399,992	205,879
TTO utility values	73,306	37,667
HUI-2 utility values	89,556	46,254
HUI-3 utility values	118,034	61,317
Transitional probability for patients with no SVR from F4 to HCC reduced to 0.0224	59,442	33,347
Transitional probability for patients with no SVR from F4 to HCC increased to 0.1304	201,764	89,245
RR of SVR for reduced-dose AVT (upper 95% confidence limit)	148,557	94,885
RR of SVR for reduced-dose AVT (lower 95% confidence limit)	89,565	42,170

AVT = antiviral therapy; ICUR = incremental cost-utility ratio; HCC = hepatocellular carcinoma; HUI-2 = Health Utilities Index Mark 2; HUI-3 = Health Utilities Index Mark 3; RR = relative risk; SVR = sustained virologic response; TTO = time trade-off.
Source: Manufacturer's pharmacoeconomic submission.

Probabilistic Sensitivity Analysis

Within the probabilistic sensitivity analysis (PSA), key parameters within the model were assigned probability distribution based on base value, uncertainty, and appropriate distribution of the uncertainty. Based on these analyses, there is some uncertainty regarding the incremental treatment effects. The probability that Scenario 1 (ELT enabling and maintenance phase) was considered cost-effective to Scenario 3 (reduced-dose AVT) under a willingness-to-pay threshold of $50,000 per QALY was reported to be 0.94% for all patients, and 36.73% for genotype 2 or 3 patients. Under a willingness-to-pay threshold of $100,000 per QALY, the probability that Scenario 1 (ELT enabling and maintenance phase) was considered cost-effective to Scenario 3 (reduced-dose AVT) was 41% for all patients, and 82% for genotype 2 or 3 patients.

CADTH Common Drug Review Reanalysis

Uncertainty Regarding Platelet Count Thresholds Required for AVT Initiation and Dose Reduction Mandated in the ENABLE Studies

Patients in the ENABLE studies were required to have platelet levels of 90,000/µL (ENABLE 1) or 100,000/µL (ENABLE 2) in order to start AVT. These thresholds have been applied in the economic model. Although Canadian product monographs for PEG-IFN-alfa-2a and -2b advise caution when starting AVT in patients with platelet counts less than 90,000 µL to 100,000 µL, and recommend PEG-IFN dosage reduction and discontinuation if platelets fall below 50,000 µL and 25,000/µL respectively, based on the most recent update of Canadian guidelines for the management of chronic HCV,[14] these limits have been challenged by experts. Experts have suggested that PEG-IFN dose reductions are not necessary until the platelet count falls below 30,000/µL, with discontinuation if the platelets fall below 20,000/µL. The clinical expert engaged in this CDR also indicated that AVT may be initiated at much lower platelet levels; therefore, the ENABLE studies may not accurately represent current clinical practice in Canada, which increases uncertainty with the economic evaluation. CDR is not able to resolve this limitation through all the reanalyses.

Dose Reduction of Antiviral Therapy Regimen

For the reduced-dose AVT regimen, the manufacturer assumed that patients with platelet counts of less than 25,000/µL will not be treated with AVT, patients with platelet counts between 25,000/µL and 50,000/µL will be treated with a dose reduction of 50% of the recommended IFN dose, and patients with platelet counts greater than 50,000/µL will be treated with a dose reduction of 75% of the recommended dose. Based on the guidelines,[14] the minimum effective dose of PEG-IFN appears to be 1 mcg/kg/week (66.7% reduction of the full dose), as opposed to 50% dose reduction applied in the economic model. CDR conducted reanalysis of the submitted model by using dose reductions in line with the Canadian guidelines.

Uncertainty Regarding Efficacy of Reduced-Dose Antiviral Therapy

The manufacturer used a relative risk of [redacted] of achieving SVR after reduced-dose AVT compared with full-dose AVT, based on an unpublished burden of illness study in Quebec. The study is a retrospective chart review study conducted in Quebec on a total 175 patients with chronic HCV, and 70 patients with TCP. The analysis was critically appraised by CDR Clinical Reviewers (CDR Clinical Report, Appendix 6), and it was found that the "reduced dose" treatment in the analysis refers to reduced duration of treatment, rather than reduced dose. Therefore, the results are not appropriate to inform the economic model. The width of the 95% CIs ([redacted] to [redacted]) confirms the uncertainty around this parameter.

As an alternative source, the relative efficacy of reduced-dose AVT versus full-dose AVT was estimated by HALT-C study,[5] using the results of 0% to 60% dose reduction group for 50% dose reduction and 61% to 97% for the 75% dose reduction. Although this study included only genotype 1 patients, CDR deemed this source to be more appropriate to inform the efficacy of reduced-dose AVT, due to the validity of the study. However, the magnitude of the applied dose reduction has been modified to reflect the Canadian guidelines.

TABLE 11: CADTH COMMON DRUG REVIEW ANALYSES: EFFICACY OF REDUCED ANTIVIRAL THERAPY DOSE

Average RR of SVR for Reduced-Dose AVT vs. Full-Dose AVT	ICUR for All Patients ($)	ICUR for Genotype 2 or 3 Patients ($)	Source
[redacted] (base-case scenario)	106,926	55,446	Manufacturer's unpublished Burden of Illness Study
[redacted] (upper 95% confidence limit)	148,557	94,885	Manufacturer's unpublished Burden of Illness Study
[redacted] (lower 95% confidence limit)	89,565	42,170	Manufacturer's unpublished Burden of Illness Study
0.51[a]	99,996	49,959	Manufacturer's derived estimate based on HALT-C study[5]
0.79[b]	122,414	70,219	CDR-derived estimate based on HALT-C study[5]

AVT = antiviral therapy; CDR = CADTH Common Drug Review; HALT-C = Hepatitis C Antiviral Long-term Treatment Against Cirrhosis; ICUR = incremental cost-utility ratio; RR = relative risk; SVR = sustained virologic response; vs. = versus.

[a] The RR = 0.51 has been estimated as a weighted average of RR = 0 (no treatment) for patients with platelet counts less than 25,000 (10% of all patients), RR = 0.28 (for 50% dose reduction) for patients with platelet counts between 25,000 and 50,000 (30% of all patients), and RR = 0.71 (for 75% dose reduction of the full dose) for patients with platelet counts more than 50,000 (60% of all patients).

[b] The RR = 0.79 has been estimated as a weighted average of RR = 0 (no treatment) for patients with platelet counts less than 25,000 (10% of all patients), RR = 0.63 (for 67% dose reduction) for patients with platelet counts between 25,000 and 50,000 (30% of all patients), and RR = 1 (no dose reduction) for patients with platelet counts more than 50,000 (60% of all patients).

Revised Long-Term Costs

The long-term chronic HCV costs were based on a study by El Saadany (2005).[2] There is a newer Canadian longitudinal cohort study by Krajden et al. (2010),[3] examining the costs associated with chronic HCV, that has also been used for the CADTH Hepatitis C Therapeutic Review.[4] The newer study resulted in significantly higher costs related to chronic HCV. CDR conducted reanalysis using the costs as reported in this study, resulting in an ICUR of $113,951 for all patients and $62,443 for genotype 2 or 3 patients.

Revised Natural History Data

The manufacturer identified several parameters estimating the natural disease progression that greatly affect the cost-effectiveness of eltrombopag. The main data source for the natural progression of the disease was HALT-C study,[5] supplemented with Townsend et al.[8] and Wright et al. studies[6] where data were not available. CADTH recently published the *Therapeutic Review of Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1*.[4] For the Therapeutic Review, data on disease progression were obtained from a systematic review conducted by Thein et al. in 2008.[7] Although there is likely some uncertainty regarding the true transition rates, these rates were generally considered acceptably robust among the currently available literature by clinical experts. CDR conducted reanalysis by implementing the natural history data from the Thein et al. study (2008), which resulted in an ICUR of $57,885 for patients with genotype 2 or 3 and $119,886 for all patients.

Time Horizon

The economic model uses a lifetime horizon of 50 years. Considering that the average baseline age of patients is 51 years, as well as the uncertainty around many parameters (such as there being no immediate clinical benefit with ELT and benefits are accrued over a long time horizon), CDR considered shorter time horizons. A 30-year time horizon was considered more appropriate for the base-case scenario.

TABLE 12: CADTH COMMON DRUG REVIEW ANALYSES: ONE-WAY SENSITIVITY ANALYSIS AROUND TIME HORIZON

Time Horizon	ICUR for All Patients ($)	ICUR for Genotype 2 or 3 Patients ($)
Base-case scenario (50 years)	106,926	55,446
10 years	399,992	205,879
20 years	156,448	81,042
30 years	**114,321**	**59,594**
40 years	107,095	55,552

ICUR = incremental cost-utility ratio.

Combination of the Above (CADTH Common Drug Review Best Estimate)

A final CDR reanalysis was conducted whereby all the reanalyses were simultaneously implemented:

- Revised AVT dose reductions
- Revised efficacy for reduced-dose AVT
- Revised chronic HCV costs
- Revised natural history of disease inputs
- Revised time horizon (30 years).

TABLE 13: CADTH COMMON DRUG REVIEW REANALYSIS BEST ESTIMATE

ELT Enabling and Maintenance Therapy vs. Reduced-Dose AVT	Difference in QALYs	Difference in LYs	Difference in Costs	ICUR - CDR Best Estimate	ICUR - Mfr Base Case
Genotype 2 or 3 patients	0.338	0.55	$30,478	$90,060	$55,446
All Patients	0.225	0.37	$37,351	$166,040	$106, 926

AVT = antiviral therapy; CDR = CADTH Common Drug Review; ELT = eltrombopag; ICUR = incremental cost-utility ratio; LY = life-year; Mfr = manufacturer; QALY = quality-adjusted life-year; vs. = versus.

CADTH Common Drug Review Price Reduction Scenarios

A reanalysis presenting the ICUR for ELT enabling and maintenance treatment versus reduced-dose AVT assuming further price reductions for ELT was conducted. A 50% price reduction under this scenario would result in ICURs less than $50,000 for patients who are genotype 2 and 3, or less than $100,000 for all patients.

TABLE 14: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BASED ON VARIOUS PRICE REDUCTION SCENARIOS ($/QUALITY-ADJUSTED LIFE-YEAR)

Scenario	ICUR			
	Based on Manufacturer's Analysis		Based on CDR Best Estimate	
	Genotype 2 or 3 Patients	All Patients	Genotype 2 or 3 Patients	All Patients
Manufacturer's base case ($2.50/tab)	$55,446	$106,926	$90,060	$166,040
10% price reduction ($2.25/tab)	$49,449	$96,940	$81,375	$150,862
20% price reduction ($2.00/tab)	$43,452	$86,954	$72,690	$135,684
30% price reduction ($1.75/tab)	$37,457	$76,969	$64,006	$120,505
40% price reduction ($1.50/tab)	$31,460	$66,984	$55,321	$105,327
50% price reduction ($1.25/tab)	$25,464	$56,999	$46,636	$90,148

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; tab = tablet.

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