Pegylated Interferon Combined with Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


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Pegylated Interferon Combined with Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation

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This report is a review of existing public literature, studies, materials and other information and documentation (collectively the “source documentation”) which are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured or represented in any way by CADTH and CADTH does not assume responsibility for the quality, propriety, inaccuracies or reasonableness of any statements, information or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.
Donald R. Husereau contributed to the development of the protocol and helped define the scope of the research project. He led the clinical review, read drafts, and provided feedback on the report. Morris Sherman provided input on the clinical content and data for the economic model. He reviewed the report and provided feedback.

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Shaila Mensinkai contributed to the development of the protocol, designed and executed all literature searches, wrote the methods section on the literature search and the associated appendix, verified and formatted bibliographic references, and reviewed the report.

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The authors are grateful to Zhiliu Tang and Marina Guimaraes Lima for assisting with the systematic review of published economic studies. They selected the studies and extracted data from selected studies. Zhiliu Tang is an assistant professor in the Department of Hospital Management at Fudan University in Shanghai, China. Marina Guimaraes Lima works in the Office of Economic Evaluation (GERAE) at the Brazilian Health Surveillance Agency (ANVISA) in Brasília, Brazil.

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Conflicts of Interest

Morris Sherman has received compensation from either the manufacturer or a competitor for conducting research and writing a publication. He is a member of the global advisory board and Canadian advisory board for Hoffmann-La Roche. He has also received speaker fees from Hoffmann-La Roche.

Uwe Siebert has received compensation from the German Federal Ministry of Health for performing a German health technology assessment. He has received compensation from the Austrian Academy of Sciences for performing an Austrian health technology assessment. He has received compensation from either the manufacturer or a competitor for conducting research.

Winnie Wong has received compensation from either the manufacturer or a competitor for conducting research and writing a publication. She has also received speaker fees or education grants, and fees for attendance at an advisory meeting.

Bruce Brady, Donald Husereau, Shaila Mensinkai, Gaetanne Murphy, and Gaby Sroczynski had no conflicts of interest to disclose. Bruce Brady works for a division in the BC Ministry of Health that is not involved in drug funding decisions.

Jeffrey Barkun conducted research in the past that had been partly funded by Roche Canada.

Chris Skedgel has conducted sponsored research for Pfizer and AstraZeneca, and has spoken at symposiums sponsored by Eli Lilly and Pfizer.
Pegylated Interferon Combined With Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation

Technology and Condition
Interferon alfa (IFN) and pegylated interferon alfa (PegIFN) in combination with ribavirin (RBV) for the treatment of chronic hepatitis C (CHC) virus infection.

Issue
Approximately 240,000 Canadians are infected with hepatitis C virus, although less than half are aware of it. The number of deaths and complications from CHC are expected to increase over the next 10 to 20 years, as is the cost of treating these complications. There is uncertainty about the costs and consequences of antiviral therapy, and a need to assess the value in funding these drugs.

Methods and Results
Clinical data on beneficial and adverse outcomes of antiviral therapy were extracted from randomized controlled trials and a previous CADTH systematic review. The net health impact was estimated using a decision-analytic model in terms of quality-adjusted life years (QALYs) and life years (LYs) saved, from the perspective of Canadian ministries of health. The analysis compared PegIFN+RBV to IFN+RBV, and to no antiviral therapy. The simulated population (base case) had an average age of 43 years, with a mix of liver disease states, hepatitis C virus genotypes, and sex, consistent with the Canadian CHC population.

Implications for Decision Making
- Antiviral therapies may improve health but are not cost saving. Compared to no therapy and after discounting future costs and effects, PegIFN+RBV was associated with 0.70 QALYs gained and $11,800 of additional lifetime costs per patient. IFN+RBV was associated with 0.51 QALYs gained and $11,500 of additional lifetime costs per patient.
- Treating mild CHC can be less effective and consumes additional resources. Compared to no therapy and after discounting future costs and effects, PegIFN+RBV was associated with 0.30 QALYs gained and $14,900 of additional lifetime costs per patient.
- Genotype, age, and disease progression rate affect the efficiency of treatment. The additional health system costs to obtain a QALY increase as the disease progression rate decreases and as the age of initiating therapy increases. Treating genotypes 2 and 3 infections costs less per QALY than treating patients with other genotypes.
- Important factors that affect optimal treatment decisions are still unknown. There are knowledge gaps about CHC, factors affecting a patient’s prognosis, and the effect of treatment on disease progression across patient subgroups.
EXECUTIVE SUMMARY

The Issue
Hepatitis C virus (HCV) infection causes chronic liver disease, and related morbidity and mortality. Available antiviral treatments include pegylated interferon (PegIFN) alfa or non-pegylated interferon (IFN) combined with ribavirin (RBV). The pegylated and non-pegylated interferons are similarly priced in Canada. In clinical trials, these therapies have demonstrated efficacy in eliminating detectable HCV from the blood, but they are also associated with serious adverse events. There is uncertainty about the impact of antiviral therapies on long-term morbidity and mortality because chronic hepatitis C (CHC) infection usually does not result in serious liver disease until decades after the initial infection. In addition, estimates of the natural progression rate of CHC infection vary. As a result, decision makers need more information about the cost-effectiveness of antiviral treatments of CHC in Canada.

Objective(s)
The objective of this report was to assess the cost-effectiveness of PegIFN plus RBV (Pegetron™ and Pegasys RBV®) to treat adults in Canada who have CHC infection. The focus was on the treatment of those who have not been treated with IFN- or PegIFN-based therapies (i.e., treatment naïve), those who have elevated alanine aminotransferase (ALT) levels, and those who are indicated for antiviral therapy (AVT) according to clinical practice guidelines in Canada. The comparators for the analysis were standard (non-Peg) IFN plus RBV, and no AVT. The cost-effectiveness of AVT in patients with mild CHC (i.e., patients with minimal to mild fibrosis and mild inflammation) was also assessed.

Clinical Review

Methods: Clinical data on the effectiveness of PegIFN+RBV and IFN+RBV were extracted from a previous CADTH systematic review. Additional data on genotype-specific virological response rates were extracted from primary studies and analyzed for each treatment strategy based on the 2000 and 2004 Canadian clinical practice guidelines.

Results: The systematic review reported no detectable difference between PegIFN+RBV and IFN+RBV in all-cause mortality or withdrawals due to adverse effects. PegIFN+RBV treatment was associated with a significantly higher rate of non-fatal serious adverse events compared to IFN+RBV (rate ratio=1.24, 95% confidence interval (CI): 1.01 to 1.51) during 48 weeks of therapy and 24 weeks of follow-up. The additional analysis of clinical data showed that PegIFN+RBV had a higher overall sustained virological response rate (i.e., viral clearance six months after completion of AVT) compared to IFN+RBV, and that genotypes 2 and 3 had higher sustained virological response rates (84% versus 69%) than other genotypes (50% versus 35%) respectively.

Economic Analysis
The economic analysis consisted of a systematic review of published economic evaluations, an original economic evaluation, and a budget impact analysis.

Methods: A cost-effectiveness and a cost-utility analysis were conducted from the perspective of publicly funded health care payers (e.g., ministries of health) in Canada. A decision-analytic Markov model was used to simulate the natural history of CHC and its treatment, based on the recommended antiviral drug regimens in the 2000 and 2004 Canadian clinical practice guidelines. Canadian data, where available, were used to populate the model. The time horizon was lifetime. Outcomes were incremental cost per life-year (LY) gained and per quality-adjusted life-year gained (QALY). Sensitivity analyses
were conducted to determine if the results were robust. Budget impact analyses were performed from the perspectives of a publicly funded Canadian drug plan and of a clinic that treats patients with CHC.

**Results:** In the base case, treatment with PegIFN+RBV was more effective and more costly ($270 in additional discounted lifetime treatment costs) than IFN+RBV. PegIFN+RBV improved health outcomes compared with IFN+RBV for life expectancy (0.26 discounted LYs gained), quality-adjusted life expectancy (0.19 discounted QALYs gained), and the long-term risk of CHC-related liver complications. Compared with no AVT, PegIFN+RBV was more effective (1.02 discounted LYs and 0.70 discounted QALYs gained) and was associated with additional lifetime treatment costs ($11,800 per patient, discounted). The discounted incremental cost-effectiveness ratios (ICER) for PegIFN+RBV compared to no AVT (the non-dominated strategy) were $17,000 per QALY gained, and $11,500 per LY gained.

In most of the sensitivity analyses, PegIFN+RBV weakly dominated IFN+RBV. The ICER results for PegIFN+RBV were most sensitive to the natural disease progression rate and the age at the start of treatment. The ICER increases as the natural disease progression rate (20-year risk of progression to cirrhosis) decreases and as the age at the start of treatment increases.

- Compared with the base case natural disease progression of 27.5%, the cost per QALY for PegIFN+RBV compared to no AVT ranged from $21,500/QALY when the progression was 20%, to $65,700/QALY at 7%, and $99,000/QALY at 4.6%.
- ICERs are $49,600/QALY when the age of treatment initiation is 61 years and about $99,200/QALY at age 68 years.

Treating patients with mild CHC was associated with a higher ICER ($56,300/QALY) than in the base case, though caution should be used when interpreting this result because no efficacy data were available on the short-term treatment impact for the patients in this simulation. The ICER for using PegIFN+RBV in the treatment of patients with genotypes 2 and 3 was lower than that for using it to treat patients with other genotypes.

These findings are consistent with those of the nine published economic evaluations that were systematically reviewed. All nine studies concluded that, on average, PegIFN+RBV was a cost-effective treatment when compared with IFN+RBV, even though in all the studies, the price of PegIFN+RBV was higher than that of IFN+RBV.

**Health Services Impact**

The incremental annual cost to a drug plan from using PegIFN+RBV in place of IFN+RBV would be about $337,000 per 100 patients treated. This assumes that an additional 10% of patients would seek treatment because of the improved virological response rate. The total discounted lifetime cost associated with the two treatment regimens is similar, given the lower costs of CHC-related complications resulting from treatment with PegIFN+RBV.

**Conclusions**

Based on our analyses, initial treatment with PegIFN+RBV, for patients with CHC and elevated ALT levels, could improve health outcomes and is associated with a lower ICER compared with IFN+RBV. The results were most sensitive to the model parameters of natural disease progression rate and the age at the start of treatment. Treatment with PegIFN+RBV is expected to result in an increase to the drug budgets of jurisdictions that already fund IFN+RBV.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AVT</td>
<td>antiviral therapy</td>
</tr>
<tr>
<td>CHC</td>
<td>chronic hepatitis C</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>ETR</td>
<td>end-of-treatment response</td>
</tr>
<tr>
<td>EVR</td>
<td>early virological response</td>
</tr>
<tr>
<td>G</td>
<td>Genotype</td>
</tr>
<tr>
<td>GEHMO</td>
<td>German hepatitis C model</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HUI</td>
<td>Health Utility Index</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ICUR</td>
<td>incremental cost-utility ratio</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon alfa</td>
</tr>
<tr>
<td>LY</td>
<td>life-year</td>
</tr>
<tr>
<td>PegIFN</td>
<td>pegylated interferon alfa</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>RBV</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>SVR</td>
<td>sustained virological response</td>
</tr>
<tr>
<td>VR</td>
<td>virological response</td>
</tr>
</tbody>
</table>
GLOSSARY

**Cirrhosis**: widespread disruption of normal liver structure (scarring of liver); process in which liver cells are damaged or killed, and replaced with scar tissue.

**Compensated cirrhosis**: condition in which heavily scarred liver can still function normally (cirrhosis without major complications).

**Decompensated cirrhosis**: condition in which extensively scarred liver cannot function normally (cirrhosis with major complications).

**EuroQoL (EQ-5D) Instrument**: instrument used to indirectly measure health-related quality-of-life preferences.

**Genotype**: genetic constitution of organism or cell; also refers to set of alleles inherited at a locus; individual’s genetic identity that does not show as outward characteristics.

**Health Utilities Index**: instrument used to indirectly measure health-related quality-of-life preferences.

**Hepatocellular carcinoma**: carcinoma of liver cells.

**Immunomodulator**: agent that affects immune system positively or negatively.

**Interferon alfa**: class of small protein and glycoprotein cytokines produced by T cells, fibroblasts, and other cells in response to viral infection, and other biological and synthetic stimuli; interferons bind to specific receptors on cell membranes; one of their effects is to inhibit viral proliferation.

**Notifiable disease**: infectious disease that must be reported to health authorities.

**Pegylated interferon alfa**: interferon conjugated with a polyethylene glycol (Peg) molecule, which reduces the elimination rate, allowing for less frequent dosing.

**Ribavirin**: broad-spectrum antiviral active against variety of DNA and RNA viruses, used with interferon alfa in treatment of chronic hepatitis C, and administered orally.

**Strong dominance**: state in which intervention is more effective and less costly than alternative intervention.

**Weak (or extended) dominance**: state in which intervention is more effective and more costly, but has lower incremental cost-effectiveness ratio than alternative intervention.
# TABLE OF CONTENTS

**EXECUTIVE SUMMARY** .......................................................................................................................... iv

**ABBREVIATIONS** ........................................................................................................................................ vi

1 **INTRODUCTION** .................................................................................................................................. 1

1.1 Background ........................................................................................................................................ 1

1.2 Overview of Technology ...................................................................................................................... 2

2 **THE ISSUE** .......................................................................................................................................... 4

3 **OBJECTIVE** .......................................................................................................................................... 5

4 **CLINICAL REVIEW** .............................................................................................................................. 6

4.1 Systematic Review of IFN-based Treatments for CHC ................................................................. 6

4.2 Methods ............................................................................................................................................ 7

4.3 Results ............................................................................................................................................... 7

5 **ECONOMIC ANALYSIS** ..................................................................................................................... 7

5.1 Review of Economic Studies ........................................................................................................... 7

5.1.1 Methods ...................................................................................................................................... 8

5.1.2 Results ...................................................................................................................................... 9

5.2 Primary Economic Evaluation ....................................................................................................... 12

5.2.1 Methods ........................................................................................................................................

5.2.2 Results ....................................................................................................................................... 18

6 **HEALTH SERVICES IMPACT** ........................................................................................................... 29

6.1 Budget Impact ................................................................................................................................... 29

6.2 Planning, Implementation, and Ethical Issues .............................................................................. 30

7 **DISCUSSION** .................................................................................................................................... 30

7.1 Summary of Results ......................................................................................................................... 30

7.1.1 Base Case results ......................................................................................................................... 31

7.2 Study Limitations ............................................................................................................................ 33

7.3 Generalizability of Findings ............................................................................................................ 35

7.3.1 Findings of Other Economic Studies ......................................................................................... 35

7.4 Health Services Impact ................................................................................................................... 36

7.5 Knowledge Gaps ............................................................................................................................. 36

8 **CONCLUSIONS** ................................................................................................................................. 37

9 **REFERENCES** .................................................................................................................................... 38

**APPENDICES – available from CADTH’s web site www.cadth.ca**

APPENDIX 1: Literature Search Strategies
APPENDIX 2: Data Extraction Form
APPENDIX 3: Figures
APPENDIX 4: Tables
1 INTRODUCTION

1.1 Background

Hepatitis C virus (HCV) infection, which causes chronic liver disease, is transmitted through contact with infected blood or body fluids and is 10 to 15 times more infectious than the human immunodeficiency virus (HIV).\(^1\,^2\) Illicit injection drug use is the primary risk factor for HCV infection in Canada, accounting for 60% of newly diagnosed infections from 1999 to 2001.\(^3\) The risk of infection through contaminated therapeutic blood products has been significantly reduced through improved screening procedures.\(^3\,^4\)

Approximately 240,000 Canadians (0.8% of the population) are infected with HCV, but only about 40% of those infected are aware of it.\(^3\,^5\) The disease is more prevalent among injection drug users, incarcerated people, First Nations people, and young street people.\(^1\,^2\)

No vaccine is available to prevent HCV infection.\(^1\) Among newly infected individuals, 15% to 25% will develop a short-term (acute) infection and spontaneously clear the virus.\(^6\) The remaining 75% to 85% develop a chronic viremia.\(^1\) The onset of liver disease is insidious, with most patients remaining largely asymptomatic for the first two or three decades after infection.\(^6\) A portion of these patients will develop serious liver complications, such as cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma, resulting in morbidity and mortality.\(^6\)

It is not possible to predict, based on clinical or epidemiologic characteristics, which acute infections will progress to persistent viremia or chronic liver disease.\(^6\) No test can be used to distinguish acute from chronic infections.\(^2\) Estimates of the life-time risk of developing cirrhosis vary. Some populations may experience a benign course and some will not progress for \(\geq 50\) years.\(^7\,^8\) An estimated 4% to 30% of patients will develop cirrhosis within 20 years.\(^8\,\) In a review of 57 CHC natural history studies, the 20-year risk of cirrhosis was 4% in a cohort of blood donors, compared with 24% in a cohort of post-transfusion patients.\(^10\) Demographic and clinical characteristics could be used to explain part of the heterogeneity, and it has been suggested that selection and referral biases may explain the remaining variation.\(^10\) An estimated 25% of patients with cirrhosis will develop decompensated cirrhosis after 10 years, and 1% to 5% will develop hepatocellular carcinoma.\(^2\,^6\,^16\)

Although hepatitis C is a notifiable disease in Canada, most of the 97,173 cases reported between 1992 and 1999 were remotely acquired infections.\(^1\,^5\) Between 1998 and 2000, to improve the detection of acute infections, the federal government established six enhanced surveillance centres, covering 15% of the population. Using data from these centres, it was determined that approximately 1,000 cases of clinically recognized acute HCV infection occur annually. Assuming that 75% to 80% of HCV infections are asymptomatic, it is estimated that 4,500 new HCV infections occur each year.\(^5\)

HCV was first identified in 1989 but it has been endemic for decades. Before it was identified, it was known as non-A, non-B hepatitis.\(^16\) Of the six known subtypes or genotypes of HCV, genotype 1 is the most common in Canada, followed by genotypes 2 and 3.\(^1\,^16\)

There is a paucity of data on the direct and indirect costs of HCV infection in Canada.\(^5\,^17\) The mortality rate due to non-A, non-B hepatitis has increased annually from 0.15 in 1993 to 0.55 in 1998 (age standardized mortality rate per 100,000).\(^5\) The 30- to 39-year-old age group has the highest reported rate of HCV infection in Canada (crude rate of \(>120\) per 100,000 in 1999).\(^5\) As a result, the
number of deaths and complications due to CHC, and the cost of treating the complications are expected to continue increasing over the next 10 to 20 years. A Canadian model has predicted that the annual health care costs of treating HCV-related disease would rise from $103 million in 2001 to $158 million in 2040.

The management options for chronically infected individuals range from lifestyle counselling to the use of antiviral therapies. The goal of antiviral therapy is to reduce the long-term risk of mortality and morbidity by slowing or preventing disease progression, reducing the risk of hepatocellular carcinoma, avoiding the need for a liver transplant, and improving the health-related quality of life. Clinical trials to date have primarily assessed intermediate or surrogate outcomes such as viral clearance. Viral clearance is determined by HCV ribonucleic acid (RNA) testing at the end of treatment or six months after the end of treatment (sustained virological response). Because most patients will not experience liver disease for decades, long-term follow-up is required to understand the impact of current antiviral therapies on morbidity and mortality.

The antiviral therapies that have been approved by Health Canada for the treatment of CHC are based on pegylated (Peg) interferon (IFN) alfa pegylated (Peg) and non-pegylated formulations (Table 1). PegIFN (alfa-2a and alfa-2b) is a slow release, longer-lasting form of traditional alfa interferons. IFN and PegIFN have been approved for monotherapy and as combination therapy with ribavirin (RBV). The manufacturers’ list prices for PegIFN+RBV and IFN+RBV range from $9,000 to $20,000 for 24 to 48 weeks of treatment respectively (Table 1).

The Canadian Consensus Conference guidelines on the treatment of viral hepatitis 2000 and 2004 provide antiviral therapy recommendations that are specific for the hepatitis C genotypes. The 2000 guidelines recommend treating chronic HCV with a combination of IFN alfa-2b plus oral RBV for 24 to 48 weeks. These guidelines were revised in 2004 after PegIFN appeared on the Canadian market. The 2004 guidelines include recommendations for stopping treatment at week 12 for genotype 1 patients who fail to demonstrate an adequate response to therapy (Appendix 3 Figure 1) (Table 2).

As of May 2006, IFN-based therapies are available in most publicly funded drug plans in Canada, often as a restricted benefit (Table 3).

1.2 Overview of Technology

IFN alfa, which is classified as a cytokine or immunomodulator, is active against viruses and malignant neoplasms. IFN is produced by cells that are infected with viruses and confers protection on uninfected cells of the same species. IFN binds to membrane receptors on the cell surface and induces enzyme systems that block viral, and possibly cellular, RNA development. It has demonstrated antiviral, antiproliferative, and immunoregulatory properties.

IFN alfa may be derived from leukocytes, lymphoblasts, or through recombinant DNA technology. IFN alfa-2a and 2b are proteins that differ by one amino acid. The conjugation of IFN with a polyethylene glycol (Peg) molecule to form PegIFN reduces the elimination rate, allowing for less frequent dosing. IFN and PegIFN are not absorbed from the gastrointestinal tract and are administered by subcutaneous injection.

RBV is a synthetic nucleoside analogue with in vitro activity against some RNA and DNA viruses. The mechanism that is used against HCV is unknown. RBV monotherapy has not demonstrated its efficacy against HCV in clinical trials. Beneficial effects are found when RBV is added to IFN or PegIFN therapy. RBV is administered orally.
IFN and PegIFN, alone or in combination with RBV, are indicated in Canada for the treatment of CHC in adult patients without cirrhosis or with compensated cirrhosis (Table 1).\textsuperscript{21} RBV, IFN, and PegIFN are available in Europe and the US.\textsuperscript{37}

### Table 1: Interferon-based treatments for CHC in Canada\textsuperscript{21,22}

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Duration of Therapy</th>
<th>Cost\textsuperscript{*} for 1 Course of Therapy (C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon Monotherapy</td>
<td>IFN alfa-2a\textsuperscript{†} (Roferon\textsuperscript{®}-A)</td>
<td>6 MIU 3 times/wk for 3 months; then 3 MIU 3 times/wk</td>
<td>24 weeks</td>
<td>$3,672</td>
</tr>
<tr>
<td></td>
<td>IFN alfa-2b (Intron A\textsuperscript{®})</td>
<td>3 MIU 3 times/wk</td>
<td>48 to 72 weeks</td>
<td>$4,894 to $7,342</td>
</tr>
<tr>
<td>Peg-Interferon Monotherapy</td>
<td>PegIFN alfa-2a (Pegasys\textsuperscript{®})</td>
<td>180 µg 1 time/wk</td>
<td>48 weeks</td>
<td>$19,000</td>
</tr>
<tr>
<td></td>
<td>PegIFN alfa-2b (Unitron Peg\textsuperscript{TM}, known as Peg-Intron\textsuperscript{TM} until January 2003)</td>
<td>1 µg/kg/wk</td>
<td>48 weeks</td>
<td>$19,000</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>PegIFN alfa-2a plus RBV (Pegasys RBV\textsuperscript{®})</td>
<td>PegIFN 180 µg/wk; RBV 800 to1,200 mg/day, based on weight and genotype</td>
<td>24 to 48 weeks</td>
<td>$9,500 to $19,000</td>
</tr>
<tr>
<td></td>
<td>IFN alfa-2b plus RBV\textsuperscript{†} (Rebetron\textsuperscript{®})</td>
<td>IFN 3 MIU 3 times/wk; RBV 1,000 to 1,200 mg/day, based on weight</td>
<td>24 to 48 weeks</td>
<td>$9,026 to $19,948</td>
</tr>
<tr>
<td></td>
<td>PegIFN alfa-2b plus RBV (Pegetron\textsuperscript{TM})</td>
<td>PegIFN 1.5 µg/kg/wk; RBV 800 to 1,200 mg/day, based on weight and genotype</td>
<td>24 to 48 weeks</td>
<td>$9,026 to $19,948</td>
</tr>
</tbody>
</table>

IFN=interferon; µg=micrograms; MIU=million international units; PegIFN=pegylated interferon; RBV=ribavirin; wk=week

\textsuperscript{*}Source for manufacturers’ list price is January 2004 edition of PPS Pharma Publications;\textsuperscript{22} excludes pharmacy mark-up and pharmacist’s professional fee; \textsuperscript{†}Product available in Canada when this project initiated has since been discontinued.\textsuperscript{23}

### Table 2: Canadian Consensus Conference guidelines on management of chronic hepatitis C (CHC) 2000 and 2004\textsuperscript{20,24}

<table>
<thead>
<tr>
<th>Genotype 1, 4, 5, or 6</th>
<th>Genotype 2 or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 Guidelines</td>
<td></td>
</tr>
<tr>
<td>Drug and dose</td>
<td>IFN alfa-2b 3 MIU sc 3 times/week, and RBV 1,000 mg daily (patients &lt;75 kg) or 1,200 mg daily (≥75 kg)*</td>
</tr>
<tr>
<td>Duration</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Early stopping rules</td>
<td>patients with positive HCV-RNA at 24 weeks should stop therapy</td>
</tr>
<tr>
<td>2004 Guidelines</td>
<td></td>
</tr>
<tr>
<td>Drug and dose</td>
<td>PegIFN alfa-2b 1.5 µg/kg sc once weekly, or PegIFN alfa-2a 180 µg sc once weekly, and RBV 1,000 mg daily (patients &lt;75 kg) or 1,200 mg daily (≥75 kg)</td>
</tr>
<tr>
<td>Duration</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Early stopping rules</td>
<td>G1 or G4, patients who fail to achieve EVR at 12 weeks should stop therapy; patients who show reduced viral load but still have detectable HCV-RNA at 12 weeks should continue therapy and be re-tested at 24 weeks; if patients still HCV-RNA positive at 24 weeks, therapy should be discontinued</td>
</tr>
</tbody>
</table>

EVR=early virological response (i.e., either undetectable HCV-RNA or at least a 1.8 log drop in HCV-RNA versus baseline); G1=genotype 1; HCV=hepatitis C virus; IFN=interferon; µg=micrograms; MIU=million international units; PegIFN=pegylated interferon; RBV=ribavirin; RNA=ribonucleic acid; sc=subcutaneous injection; * IFN monotherapy recommended for patients who cannot tolerate RBV (e.g., due to anemia)
Table 3: Formulary status of IFN-based therapies for CHC in publicly funded drug plans in Canada*

<table>
<thead>
<tr>
<th>Drug Generic Name (Brand Name)</th>
<th>BC</th>
<th>AB</th>
<th>SK</th>
<th>MB</th>
<th>ON†</th>
<th>QC</th>
<th>NL</th>
<th>NB</th>
<th>NS</th>
<th>PE</th>
<th>YT</th>
<th>NIHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN alfa-2b (Intron A®)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>F</td>
</tr>
<tr>
<td>PegIFN alfa-2b (Unitron PegTM)</td>
<td>N</td>
<td>R</td>
<td>R</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PegIFN alfa-2a (Pegasys®)</td>
<td>N</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>N</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>PegIFN alfa-2b + RBV (PegetronTM)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>N</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PegIFN alfa-2a + RBV (Pegasys RBV®)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>N</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

F = listed on formulary as full benefit; IFN = interferon; N = not listed or excluded from formulary; PegIFN = pegylated interferon; R = restricted or exception status (i.e., patients must meet clinical criteria); RBV = ribavirin; U = under review.

* Source: (Patrick Crawford, Social Services and Seniors, Charlottetown: personal communication, 2006 May 25), and online formularies.25-36; †May be available through Section 8 (individual clinical review mechanism); ‡Limited use criteria exclude treatment of CHC.

Table 4 summarizes the adverse effects resulting from the use of IFN, PegIFN, and RBV. Some serious adverse effects may lead to dose reductions or discontinuation of therapy. In one randomized trial, adverse effects caused 34% and 13% of patients treated with IFN, and 42% and 14% of patients treated with PegIFN combination therapy to reduce drug dosage or stop therapy respectively (p values not reported).38

Table 4: Adverse effects associated with IFN alfa and RBV37,39

<table>
<thead>
<tr>
<th>IFN or PegIFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like symptoms (e.g., fatigue, headache, fever, myalgia, rigors); gastrointestinal symptoms (e.g., nausea, diarrhea, anorexia); depression or other neuropsychiatric symptoms; neutropenia, infection; thrombocytopenia, anemia; skin rash; thyroiditis; exacerbation of autoimmune disorders</td>
<td>Hemolytic anemia; teratogen; skin rash</td>
</tr>
</tbody>
</table>

IFN = interferon; PegIFN = pegylated interferon; RBV = ribavirin

2 THE ISSUE

HCV infection causes chronic liver disease, and associated morbidity and mortality. It is thought that almost a quarter of a million Canadians are infected with HCV, but only about 40% realize it.

According to the 2004 Canadian Consensus Conference guidelines on the management of viral hepatitis, all CHC patients should be assessed for AVT, regardless of the stage of their liver disease. The decision to treat should be based on factors such as the risk of liver disease progression, the likelihood of treatment response, the risk of adverse effects, the patient’s symptoms, and the patient’s wishes.20 There should be a reasonable expectation that the patient will comply with therapy and abstain from alcohol and injection drug use. Because of RBV’s teratogenic potential, patients must use adequate contraception. The decision to treat is complex, because many of these factors are difficult to assess. In addition, a decision must be made regarding when to start therapy (e.g., whether to initiate in patients with mild liver disease), because the disease may not progress for decades.

Policy makers must assess the relative benefits, harms, and costs of treatment when considering funding decisions. In Canada, the price of PegetronTM and that of Pegasys RBV® are each equal to...
the price of the combination IFN+RBV product (Rebetron®). Therefore, an uncritical decision would be to select the drug combination that leads to improved short-term outcomes. However, this assumes that antiviral therapy (AVT) is cost-effective compared to no AVT treatment, and it ignores the financial and health costs associated with any adverse events. It also ignores the uncertainties about CHC —the natural disease progression varies from person to person — and the impact of the drug regimens on progression. There is uncertainty about whether the immediate effects of treatment (i.e., sustained virological response) reduce morbidity and mortality from related liver disease in the very long term.

3 OBJECTIVE

The objective of this report is to assess the cost-effectiveness of PegIFN plus RBV to treat adults in Canada who have chronic HCV infection. The focus will be on the treatment of those who:
- have not been treated previously with PegIFN or IFN-based therapies (i.e., treatment-naïve patients)
- have elevated alanine aminotransferase (ALT) levels
- are indicated for AVT according to clinical practice guidelines in Canada.

The comparators for the analysis are:
- standard (non-pegylated) IFN plus RBV
- no antiviral treatment (no AVT).

The report addresses the following research questions:
- What is the cost-effectiveness, from a Canadian public payer perspective, of treating patients with CHC infection using PegIFN combined with RBV, compared with IFN combined with RBV, and compared with no AVT? Are the HCV treatment management strategies in the 2004 Canadian clinical practice guidelines cost-effective? How cost-effective are genotype-specific guidelines for dosing and duration of treatment and rules for stopping treatment?
- What is the cost-effectiveness, from a Canadian public payer perspective, of treating patients with mild CHC infection using PegIFN combined with RBV, compared with IFN plus RBV, and compared with no AVT?

The economic analysis consists of two parts: a systematic review of published economic evaluations of PegIFN+RBV compared with standard IFN+RBV for the treatment of chronic HCV infection, and an original economic evaluation addressing the research questions just cited.

There is a commentary on the health services impact of providing coverage for PegIFN therapy, including the budget impact for public payer drug plans and the health care system.

The clinical and surrogate outcomes of the therapies are quantified, drawing on previous work by CADTH. The report takes into account the cost of the therapies and the associated adverse events. Where available, Canadian data on costs, resource use, epidemiology, and clinical practice are used.

Although there is interest in other research questions, including the treatment of other subpopulations (e.g., treatment relapers or non-responders, those with co-morbidities such as HIV co-infection, or those with HCV risk factors such as injection drug users), these questions will not be addressed because of limitations in the data available and modelling complexities.

The conduct of the economic analysis was based on a protocol written a priori.
4 CLINICAL REVIEW

In 2004, CADTH completed a systematic review that examined the effectiveness of IFN-based therapies.39 The results of the systematic review, with additional data extracted from other clinical studies, form the basis of this clinical review. Some data from this section were included in the economic analysis.

4.1 Systematic Review of IFN-based Treatments for CHC

The objective of the systematic review39 was to evaluate the mortality and serious morbidity of patients with CHC infection, when comparing IFN+RBV versus IFN, and IFN+RBV versus PegIFN+RBV. Withdrawals due to adverse events, quality of life, and virologic markers related to treatment were also considered.

Of the trials identified, 51 (n=7,474) compared IFN+RBV with IFN, and two trials38,40 (n=2,729) compared PegIFN+RBV with IFN+RBV. Data were analyzed on an intention-to-treat basis.

The systematic review reported no detectable difference between PegIFN+RBV and IFN+RBV in withdrawals due to adverse events (fixed effect estimate of relative risk 0.97, 95% confidence interval (CI): 0.75 to 1.24) or in all-cause mortality. The PegIFN+RBV treatment was associated with a significantly higher rate of non-fatal serious adverse events compared to IFN+RBV (rate ratio=1.24, 95% CI: 1.01 to 1.51) during 48 weeks of therapy and 24 weeks of follow-up. Table 5 summarizes the serious adverse events observed in the included randomized controlled trials (RCTs).39

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Incidence of Serious Adverse Events, Number (%)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric event</td>
<td>PegIFN alfa-2a or 2b +RBV, n=1,519</td>
<td>IFN alfa-2b +RBV, n=983</td>
</tr>
<tr>
<td>Serious infection</td>
<td>50 (3.3)</td>
<td>29 (3.0)</td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>30 (2.0)</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td>All other serious adverse events, each occurring in &lt;1% of patients</td>
<td>168 (11.1)</td>
<td>76 (7.7)</td>
</tr>
</tbody>
</table>

IFN=Interferon; RBV=ribavirin; PegIFN=pegylated interferon

PegIFN+RBV increased the chance of achieving a SVR by 17% (relative risk 1.17, 95% CI: 1.07 to 1.27) compared to IFN+RBV. Thus, one additional patient avoided persistent viremia for every 14 treated with PegIFN+RBV instead of IFN+RBV.39

The systematic review concluded the following:
- “Information on the quality or quantity of life related to IFN-based treatment is lacking.
- Morbidity and mortality after therapy with RBV added to standard IFN could not be estimated from the randomized trial evidence.
- PegIFN combined with RBV can increase the need for urgent medical attention when compared to IFN+RBV
- PegIFN+RBV therapy can reduce the risk of persistent viremia and liver enzyme elevation to the greatest degree, when it is compared with IFN+RBV or with IFN therapy alone.”39
Refer to CADTH Technology Report 47,\textsuperscript{39} Interferon-based therapies for chronic HCV infections: an assessment of clinical outcomes, for a description of study methods and results.

### 4.2 Methods

For our economic model, genotype-specific virological response rates were required for the dosages and therapy time-points (e.g., 12, 24, 48, and 72 weeks) of each treatment strategy, as stated in the Canadian Consensus Conference guidelines.\textsuperscript{20,24} Because this information was unavailable from the CADTH systematic review, additional data extraction and analysis were required.

Virological response rates were extracted from the RCTs identified in the systematic review,\textsuperscript{38,40-43} and from studies that were identified through additional literature searching and consultation with experts (Ferenci et al.,\textsuperscript{44} Poynard et al.,\textsuperscript{45} and Hadziyannis et al.\textsuperscript{46}). Appendix 4 Table 1 provides a summary of the included studies.

The data extracted from the RCTs appear in Appendix 4 Table 2. Virological response rates from multiple studies were combined through weighted pooling based on sample size. Virological response rates for all the time-points were unavailable from the primary RCTs. As a result, some endpoints were imputed (Appendix 4 Table 2).

### 4.3 Results

Table 6 shows the adjusted virological response rates at 12 to 72 weeks that were incorporated into the economic model.

<table>
<thead>
<tr>
<th></th>
<th>Overall*</th>
<th>HCV genotype other than 2 or 3VR % (number with VR/sample size)</th>
<th>HCV genotype 2 or 3 VR % (number with VR/sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN+RBV</td>
<td>SVR</td>
<td>61% (253/298)</td>
<td>84% (81/96)</td>
</tr>
<tr>
<td></td>
<td>12 wks</td>
<td>85% (89/118)</td>
<td>75% (90/96)</td>
</tr>
<tr>
<td></td>
<td>24 wks</td>
<td>75% (182/271)</td>
<td>48% (298/593)</td>
</tr>
<tr>
<td></td>
<td>48 wks</td>
<td>67% (278/655)</td>
<td>67% (227/593)</td>
</tr>
<tr>
<td></td>
<td>72 wks</td>
<td>50% (227/593)</td>
<td>42% (278/655)</td>
</tr>
<tr>
<td></td>
<td>48 wks</td>
<td>94% (247/291)</td>
<td>85% (227/593)</td>
</tr>
<tr>
<td>IFN+ RBV</td>
<td>SVR</td>
<td>45% no data</td>
<td>69% (201/291)</td>
</tr>
<tr>
<td></td>
<td>12 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72 wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on Canadian genotype distribution in cohort (31% genotypes 2 or 3). ETR=end-of-treatment response; PegIFN=pegylated interferon; RBV=ribavirin; SVR=sustained virological response 24 weeks after end of treatment; VR=virological response

### 5 ECONOMIC ANALYSIS

#### 5.1 Review of Economic Studies

A systematic review was performed on the cost-effectiveness of PegIFN+RBV compared with IFN+RBV for the treatment of adults with CHC infection; and the economic evidence was appraised according to CADTH’s guidelines for authors.\textsuperscript{47} The results obtained from the systematic review were considered in the design of the primary economic analysis.
5.1.1 Methods

a) Literature search strategy
Published literature was obtained by performing a multi-file OneSearch® of MEDLINE®, EMBASE®, BIOSIS Previews®, PASCAL, and International Pharmaceutical Abstracts on the DIALOG® system in July 2003. The search strategy included appropriate descriptors, keywords, registry numbers, and generic and trade names of the drugs. An economic filter was used to restrict retrieval to relevant economic studies. Regular database alerts were set up until January 2006. Parallel searches were performed and updated on PubMed and the Cochrane Library. The last PubMed update was performed in January 2006, and the last Cochrane Library update was performed in Issue 1, The Cochrane Library, 2006. A broader search was performed in the Health Economics Evaluations Database (HEED). The last update was performed in January 2006. The detailed literature search strategy appears in Appendix 1.

Grey literature was retrieved by searching the web sites of regulatory agencies, health technology assessment and related agencies, trial registries, and specialized databases, such as those of the University of York NHS Centre for Reviews and Dissemination. Conference abstracts were obtained by searching the web sites of liver and gastroenterology associations such as the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), American Gastroenterological Association (AGA), and the annual Digestive Disease Week (DDW) conference.

Additional information was sought by searching bibliographies of retrieved reports and by contacting experts (MS, US, WW).

b) Selection criteria
A study was eligible for inclusion in the review if it met each of the following criteria:

- **study design** is full economic evaluation, defined as the comparative analysis of the costs and outcomes of alternative health care interventions; includes cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost-minimization analysis
- **population** of treatment-naïve adults with CHC infection
- **intervention and comparator** are PegIFN+RBV versus IFN+RBV; both versions of PegIFN+RBV (i.e., alfa-2a and alfa-2b) were considered.

c) Selection method
Two reviewers (ZT and ML) independently screened citation titles and abstracts, and selected those for full paper review. Any disagreement was resolved through consensus. (Screening of alerts occurring later in the process was undertaken by BB or GM.)

d) Data extraction and abstraction strategy
Two reviewers (ZT and ML) independently extracted relevant information from the selected studies using the form in Appendix 2. Uncertainty or disagreement about any item on the form was resolved by consulting the original paper for clarification, and if necessary, discussing the issue with a third party (BB). (Information from studies selected later in the process was extracted by BB.) No formal quality assessment of the studies was performed, even though study limitations or weaknesses were noted during the data extraction process.
e) **Data analysis methods**

Study characteristics and results were described in a narrative synthesis. Differences were noted between studies in terms of methods or data inputs (e.g., treatment management algorithm, relative prices of the alternative therapies). In addition, the limitations and transparency of each study were noted during the extraction process.

The results are presented in terms of incremental cost per quality-adjusted life-years (QALYs), based on the currency used in each study. Information on the magnitude of the health benefit of the intervention, in terms of the discounted QALYs gained, is presented with the results of the sensitivity analyses and subgroup analyses.

5.1.2 **Results**

a) **Literature search**

Appendix 3 Figure 2 shows the selection of full papers included in the review. The literature search identified 148 records (abstracts and titles), of which 78 papers were retrieved for further review. Of these, nine full papers reporting on nine separate studies met the inclusion criteria. The reasons for excluding 69 retrieved papers are given in Appendix 3 Figure 2.

b) **Study characteristics**

Appendix 4 Table 3 summarizes some key characteristics of the nine studies.

**Funding source**

Funding for six studies was provided by the manufacturers of the drugs: Roche\textsuperscript{48-50} and Schering-Plough.\textsuperscript{51-53} Three studies\textsuperscript{54-56} were funded independently of the manufacturers, two\textsuperscript{54,55} of which evaluated both PegIFN products.

**Intervention and comparator**

**Intervention:** Three studies\textsuperscript{48-50} evaluated PegIFN alfa-2a+RBV, and four studies\textsuperscript{51-53,56} evaluated PegIFN alfa-2b+RBV. The studies by Shepherd\textsuperscript{54} and Siebert\textsuperscript{55} evaluated both treatments.

**Comparator:** The comparator in all studies was IFN alfa-2b+RBV. Six studies included other comparators: no AVT,\textsuperscript{51,53-56} IFN monotherapy,\textsuperscript{50,54-56} and PegIFN monotherapy.\textsuperscript{54}

**Treatment management strategy (for PegIFN+RBV and IFN alfa-2b+RBV):** The duration of treatment in all studies was 48 weeks. Four studies\textsuperscript{48-50,56} conducted a separate evaluation of the 24-week treatment duration for patients with genotypes 2 and 3 (G2+3) or G non-1. With regard to the 48-week treatment strategy, two studies\textsuperscript{52,54} did not include stopping rules, three studies\textsuperscript{51,55,56} included a 24-week stopping rule, and three studies\textsuperscript{48-50} included a 12-week stopping rule for PegIFN+RBV and a 24-week stopping rule for the IFN+RBV. The study by Wong\textsuperscript{53} evaluated >1 48-week treatment strategy.

**Direct costs of intervention and comparator:** The relative cost of PegIFN+RBV versus IFN+RBV is a factor that is used to determine the cost-effectiveness of the intervention. All studies except for Buti et al.\textsuperscript{52} reported the cost of the drugs. Three studies\textsuperscript{48,51,56} reported that the cost of PegIFN+RBV was 17% to 47% higher than that of IFN+RBV. The remaining five studies reported that the cost of PegIFN+RBV was 54% to 110% higher than that of IFN+RBV. Drug treatment costs varied across studies based on the duration of treatment (based on genotype), the management strategy (stopping...
rules), and the dosing of RBV (based on the patient’s weight or fixed at 800 mg/day). In no study were the prices the same for PegIFN+RBV and IFN+RBV, as is the case in Canada.

**Population**
All studies evaluated adults with CHC. In seven studies, the patients were treatment-naïve; this was unclear in the studies by Shepherd\(^54\) and Annemans\(^50\). The studies tended to focus on patients with mild or moderate CHC without comorbidities, complications, or cirrhosis, although one study\(^54\) focused on patients with moderate to severe CHC. The Salomon study\(^56\) focused on patients with mild CHC. Three studies\(^51-53\) did not provide information about complications, comorbidities, or severity of CHC.

**Study design**

*Location:* Three studies were set in the US\(^48,53,56\), the others in Europe (Germany,\(^51,55\) UK,\(^54\) Spain,\(^52\) Italy,\(^49\) and Belgium\(^50\)).

*Perspective:* Six studies used a health care payer perspective, while the other three\(^51,53,55\) used the health care payer perspective combined with some direct costs to the patient. Some studies mislabelled this perspective as “societal.”

*Time horizon:* Seven studies used a lifetime horizon. The Shepherd study\(^54\) used a 30-year time horizon, and the Annemans study\(^50\) used a 25-year time horizon.

*Discount rate:* Seven studies used a discount rate of 3% for costs and health outcomes. The Shepherd study\(^54\) discounted costs at 6% and health outcomes at 1.5%. The Annemans study\(^50\) did not specify the discount rate.

*Risk of progression to cirrhosis:* One parameter that was used in the models was the natural history of HCV infection, specifically the risk of progression to compensated cirrhosis and other liver complications. To model disease progression, the studies used populations with different characteristics, disease severity, and stages of disease. The studies also reported the risk of progression to cirrhosis in different ways:

- Four studies\(^48-50,52\) used an annual probability of cirrhosis of 0.073 for a population with moderate CHC or CHC and no cirrhosis, whereas the Shepherd study\(^54\) used an annual probability of 0.01 for those with moderate or severe CHC.
- Three studies reported a 20-year risk of cirrhosis. The Wong\(^53\) study predicted a 23% risk of cirrhosis in 20 years for a population with predominately moderate CHC. Siebert\(^51\) and Siebert\(^55\) predicted a 19% risk for a population with initially mild CHC adjusted for spontaneous remission.
- The Salomon\(^56\) study used a 30-year risk of cirrhosis for those with CHC and no fibrosis ranging from 13% to 46% (30% average) for men and 1% to 29% (9% average) for women.
- All but one study\(^54\) conducted a sensitivity analysis of the rate of progression to cirrhosis.

**Other study characteristics** (not shown in Appendix 4 Table 3)

*Type of economic evaluation:* All studies reported results for cost per QALY gained (i.e., cost-utility analysis). Four studies\(^49,52,55,56\) also reported results for cost per life-years (LY) saved.

*Model:* All studies used a Markov model to conduct the analysis.
Health outcomes: The clinical trials reported by Manns et al.\textsuperscript{38} or Fried et al.\textsuperscript{40} were the source of the treatment response data used in the models of all nine studies. Two studies\textsuperscript{50,56} supplemented these data with data from other clinical papers. The model in three studies\textsuperscript{51,55,56} also included the disutility of the adverse events associated with the treatments.

Sensitivity analysis: All studies reported results for deterministic sensitivity analysis (no probabilistic sensitivity analysis was performed). Two studies\textsuperscript{51,52} reported the threshold age for cost-effective use of the treatments, and one study\textsuperscript{54} conducted a sensitivity analysis using high and low viral loads.

c) Economic results

Overall results:
- All nine studies concluded that, on average, PegIFN+RBV is cost-effective (i.e., associated with better outcomes and more costs, but at a cost per outcome below a threshold) for patients with CHC compared with IFN+RBV. The cost-effectiveness threshold was stated in six studies. It ranged from €20,000 to €50,000 per QALY gained and US$50,000 per LY saved in one case.
- The results of the sensitivity and subgroup analysis were robust (i.e., less than the cost-effectiveness threshold) in all the cases analyzed in five studies.\textsuperscript{48,49,51,52,55} In the other studies, the results of the sensitivity and subgroup analysis were generally cost-effective.

Additional comments on results for PegIFN alfa-2a+RBV:
- The Sullivan study\textsuperscript{49} concluded that this regimen was cost-effective regardless of the genotype and under a range of assumptions.
- Four studies\textsuperscript{48-50,54} showed the base case ICER was lower for G2+3 (or G non-1) versus G1 (or G1,4,5,6). The Sullivan study\textsuperscript{48} found that the pegylated regimen was dominant (i.e., less costly and more effective) for treating patients with G2+3 compared to treatment with IFN alfa-2b+RBV.
- The Annemans study\textsuperscript{50} found that results for patients with G1,4,5,6 were sensitive (i.e., above the cost-effectiveness threshold) to lower disease progression probabilities (e.g., cirrhosis 1\% versus 7.3\%) and higher utility values for disease states.
- The Sullivan study\textsuperscript{48} concluded that a 24-week (versus 48-week) treatment duration for patients infected with G2+3 is cost-effective.

Additional comments on results for PegIFN alfa-2b+RBV:
- The Salomon study\textsuperscript{56} concluded that, on average, PegIFN alfa-2b+RBV was cost-effective (US$35,000 per QALY or about C$44,000 per QALY equivalent) but that the ICER results vary between subgroups and depend on model assumptions. The results were found to be sensitive to plausible assumptions about the utility for patients with mild to moderate CHC and the disutility of adverse events associated with treatment. The results were high for women versus men (ICER is about 60\% higher for women) and for women with G1 HCV infection (US$55,000 per QALY). This seems to be at odds with the Shepherd study\textsuperscript{54} which showed a high ICER (£37,600 per QALY) for patients with G2+3 HCV who were treated with PegIFN alfa-2b+RBV, given the low improvement in SVR for patients treated with PegIFN alfa-2b+RBV (82\%) versus IFN+RBV (79\%).
- The studies by Siebert,\textsuperscript{51} Buti,\textsuperscript{52} and Wong\textsuperscript{53} showed that the ICER was lower for the RBV weight-based regimen versus the RBV fixed-dose regimen. The studies by Buti\textsuperscript{52} and Wong\textsuperscript{53} concluded that PegIFN alfa-2b+weight-based RBV is cost-effective compared to the fixed dose.
The Siebert study\textsuperscript{51} concluded that the weight-based and the fixed-dose regimens are cost-effective compared to IFN+RBV.

- The Wong study\textsuperscript{53} concluded that a 12-week (with a 24-week) stopping rule for patients with G1 HCV is cost-effective, though a 12-week stopping rule may be unnecessary for patients with G2+3, given the high SVR rates. The study also found that a sensitivity analysis that used a 9% risk of cirrhosis over 20 years (versus 23% in the base case) pushed the ICER above US$50,000 per QALY.

**Health outcomes:**

- There is a range of QALYs gained in the economic analyses that are based on the same clinical study (Manns,\textsuperscript{38} Fried,\textsuperscript{40} or both). The reasons for the differences between the high and low values of the ranges when comparing the economic studies with each other were not apparent.
- The discounted QALYs gained for economic studies based on the Manns study (PegIFN alfa-2b+RBV)\textsuperscript{51,52} were less than those based on the Fried study (PegIFN alfa-2a)\textsuperscript{48-50} In the Manns and Fried studies, the comparator was IFN alfa-2b+RBV.
- In the economic analyses based on the Fried study (i.e., PegIFN alfa-2a+RBV),\textsuperscript{48-50} the discounted QALYs gained for the G2+3 subgroup are greater than those for the G1,4,5,6 subgroup. In the analyses based on the Manns study (i.e., PegIFN alfa-2b+RBV),\textsuperscript{52} the discounted QALYs gained for the G2+3 subgroup are less than those for the G1,4,5,6 subgroup (by a factor of \( \geq 50\% \)).
- In the analyses based on the Manns study,\textsuperscript{51,52} the PegIFN alfa-2b+weight-based RBV regimen gained more QALYs (by a factor of \( \geq 2 \)) than the fixed-based dosing (800 mg) regimen.

**5.2 Primary Economic Evaluation**

**5.2.1 Methods**

\textit{a) Model structure}

The economic evaluation was conducted using a decision-analytic Markov model to simulate the natural history of CHC and its treatment using antiviral drug regimens. A modified version of the German Hepatitis C Model (GEHMO), which was originally commissioned by the German Federal Ministry of Health for a health technology assessment,\textsuperscript{55} was used. This revised model is the result of a formal collaboration agreement between CADTH and the German Agency for Health Technology Assessment (DAHTA) at the German Institute of Medical Documentation and Information (DIMDI), German Federal Ministry of Health.

The GEHMO was based on a published and validated Markov model.\textsuperscript{55,57,59} For this report, the GEHMO was modified to simulate clinical practice under the 2004 Canadian HCV clinical practice guidelines and the impact of treatment-related serious adverse events. Available epidemiological, clinical, resource use, and unit cost data for Canada were used in the model. The model structure, parameter values, and assumptions were checked by clinical experts from Canada (MS and WW).

The model (Figure 1) compares the long-term health outcomes (including remaining life expectancy and quality-adjusted life expectancy) and lifetime costs associated with the evaluated strategies. The costs and outcomes are then calculated using the relevant probabilities to estimate their expected values. The incremental results of the strategies are based on the differences in these expected values.
Each circle in Figure 1 represents a health state of a patient with chronic hepatitis C. Each arrow represents possible transitions between health states, which may occur each year. Dotted arrows represent lower transition probabilities, reflecting the viral negative state. The two boxes represent the target population defined by histological states and separated by viral-positive and viral-negative status. Histology-specific rates for no response, relapse after response, and sustained response after AVT are applied to the three viral-positive health states (mild hepatitis, moderate hepatitis, and compensated cirrhosis). Separated states were considered for liver diseases from decompensated cirrhosis: variceal hemorrhage, hepatic encephalopathy, and liver transplant, separated into the first year and subsequent years; and ascites: diuretic-sensitive and diuretic-refractory ascites. Individuals in any health state may die from causes related to their age and sex, similar to what occurs in the general Canadian population, and individuals with decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation may die from liver-related causes.

The model simulates the impact of treatment effects (i.e., SVR) on health outcomes by altering the risk of progression through the CHC-related health states. Successfully treated patients (i.e., those who achieve HCV-negative status) with mild CHC have no risk of disease progression compared with HCV-positive patients. HCV-negative patients with moderate CHC or compensated cirrhosis have a reduced risk of transitioning to more severe health states.

**Figure 1: Decision-analytic Markov model**

RNA=ribonucleic acid
**b) Methods and model parameters**

**Type of economic evaluation:** Two types of economic evaluation were conducted: a cost-effectiveness analysis and a cost-utility analysis.

**Target population:** The population analyzed in the model are Canadian adults with CHC infection who have not been treated with PegIFN or IFN-based therapies (i.e., treatment naïve), and have elevated ALT levels.

The population characteristics (Appendix 4 Table 4) were based on data for Canadians or on calculations based on Canadian data:

- average age of 43 years
- 52.3% mild CHC, 28.4% moderate CHC, and 19.3% compensated cirrhosis
- 31% genotype 2+3
- 34% females.

The histological classification as mild or moderate CHC, or compensated cirrhosis was defined by the modified histology activity index of Knodell.\(^{60,61}\) In the absence of cirrhosis, a Knodell periportal inflammation score of 0 to 1 defined mild CHC, and a score of 3 to 10 defined moderate CHC. Regardless of the Knodell inflammation score, a Knodell fibrosis score of 4 defined CHC with cirrhosis.

**Intervention and comparators:** The following strategies were evaluated:

- no antiviral therapy (no AVT)
- IFN alfa-2b (3 MIU three times per week) plus RBV (1,000 mg/day to 1,200 mg/day), according to the 2000 Canadian practice guidelines\(^ {24}\)
- PegIFN (180 \(\mu\)g per week for PegIFN alfa-2a, 1.5 \(\mu\)g/kg per week for PegIFN alfa-2b) plus RBV (800 mg/day to 1,200 mg/day) with dosage and treatment duration set according to the 2004 Canadian practice guidelines.\(^ {20}\)

In the second strategy, IFN+RBV was given for 24 weeks in patients with HCV genotypes 2 and 3 (G2+3) and for an intended period of 48 weeks in patients with other genotypes (G1,4,5,6). In patients with G2+3, no testing or early stopping was required before the end of AVT. Patients with other genotypes were tested after 24 weeks of AVT, and AVT was stopped if no virological response (i.e., still HCV-RNA positive) was observed (Table 2).\(^ {24}\)

In the third strategy, patients with G2+3 were treated with PegIFN+RBV (800mg/day) for 24 weeks, with no testing or stopping of AVT before the end of 24 weeks. Patients with other genotypes were treated with PegIFN+RBV (1000 mg/day to 1200 mg/day) for an intended period of 48 weeks. Patients were tested at 12 weeks, and AVT was stopped if there was no early virological response (drop of viral load by less than 2 million copies or a detected viral load). Patients continuing AVT were tested again at 24 weeks, and those with an undetected viral load continued AVT to 48 weeks, whereas patients with a detected viral load stopped AVT at 24 weeks.

Differences, if any, between the two versions of PegIFN (alfa-2a and alfa-2b) have not been evaluated in this report.
**Perspective:** The perspective is publicly funded health care payers in Canada (e.g., ministries of health). Therefore, only the direct, publicly funded health care costs are considered. Small out-of-pocket expenses that are incurred by patients are included, as specified in the CADTH guidelines.

**Time horizon:** A lifetime time horizon was simulated (i.e., all patients were followed until death from CHC-related diseases or other causes). This captures all relevant clinical and economic outcomes, including hospitalization, liver transplant, and death due to CHC-related liver disease; and permits the treatment strategies to be fully evaluated. In the model, short-term surrogate outcomes (i.e., SVR) were linked and extrapolated to long-term health outcomes (e.g., complications due to advanced liver disease and mortality).

**Health outcomes:** In the model, health outcomes are defined in terms of effects of treatment, adverse events, CHC-related health states (including the associated quality of life) and life expectancy.

- The evidence of treatment effectiveness is based on the analysis of treatment efficacy, as shown in the clinical trials. In the model, the virological response to treatment includes SVR, no response (treatment failure), and response and relapse. SVR, the primary efficacy endpoint in the trials, is the maintenance of viral clearance (undetectable HCV-RNA) for at least 24 weeks after treatment stops. The model also includes the possibility of spontaneous remission of CHC.

- Treatment-related adverse events were included in the model where they were significantly different between the two treatment regimens. Table 5 from Husereau showed that PegIFN+RBV led to a significantly greater incidence of two categories of adverse events compared to IFN+RBV: serious infections [e.g., cellulitis, abscess, appendicitis: absolute rate 2.6% versus 1.1%, with a rate ratio of 2.36 (95% CI: 1.21, 4.59)], and all other serious adverse events experienced by \( \leq 1\% \) of the trial population [11.1% versus 7.7%, with a rate ratio of 1.43 (95% CI: 1.09,1.88)]. Any differences in adverse events between AVT and no AVT (i.e., placebo) were excluded in the model except for the short-term utility reduction assigned during AVT.

- The health states that are associated with CHC are shown in Appendix 4 Table 5. The states include mild and moderate CHC, CHC-related compensated cirrhosis, liver diseases due to decompensation (including esophageal variceal hemorrhage, hepatic encephalopathy, and ascites, separated into diuretic-sensitive and diuretic-refractory ascites), hepatocellular carcinoma, liver transplantation (separated into first year and subsequent years), and death. The histological classification as mild or moderate CHC or compensated cirrhosis was defined by a modified histology activity index. The base case analysis does not consider liver transplantation for patients with hepatocellular carcinoma or re-transplantation for patients with prior liver transplantation. Transplantation for hepatocellular carcinoma was included in the sensitivity analysis (Table 10 sensitivity analysis 5). Appendix 4 Table 5 shows the annual transition probabilities between the health states, reflecting the natural history of CHC. The natural history data were taken from the published studies shown in the table. In the model, patients who become HCV-negative (spontaneously or through AVT) progress to more severe health states. Appendix 4 Table 5 shows the odds ratios associated with HCV-negative patients that were applied to the annual probabilities of transitioning to more severe health states. Progression rates for HCV-positive patients were multiplied by these odds ratios and re-transformed into probabilities to obtain progression rates for viral negative disease in the model.

- The model separates deaths caused by CHC-related diseases and deaths from other causes. Appendix 4 Table 5 shows the probability of death due to CHC-related liver disease and liver
transplantation. The life expectancy of those patients not dying from CHC-related diseases is based on the application of age- and sex-specific Life Tables for Canada, 1995-1997.63

Valuation of health outcomes: The health-related quality of life for the CHC-related health states and treatment effects (i.e., SVR and adverse events) was measured in terms of preference-based utilities (Appendix 4 Table 6). The utility scores were empirically derived for a Canadian CHC population in two studies using the Health Utilities Index (HUI).64,65 The utility scores were then combined with life-years in the respective health states to estimate QALYs.

The utility scores for death and perfect health were set at 0.0 and 1.0 respectively. Appendix 4 Table 6 shows the absolute short-term utility decrement of 0.14 due to adverse events experienced during AVT65 and the absolute short-term utility increment of 0.04 for patients with SVR (assumed to be of one-year duration in the base case). Additional details relating to the derivation of the utility scores appear in Appendix 4 Table 6.

Resource use and costs: All economically significant direct health care costs incurred by the public payer were included in the analysis.

- Appendix 4 Table 7: annual treatment costs of CHC-related health states
- Appendix 4 Table 8: antiviral drug costs
- Appendix 4 Table 9: cumulative costs associated with one course of AVT (excluding the costs of antiviral drugs and HCV-RNA tests).

The costs in the three tables were estimated using a micro-costing method. Data on resource use and unit costs were based on data for Canada from the literature, health care databases, clinical practice guidelines, and expert opinion. Resource use associated with the three strategies included hospitalization, outpatient visits, diagnostic and laboratory testing, medication, and procedures related to the specific health states. All historical costs were inflated to 2004 Canadian dollars using the Canadian Consumer Price Index.

The costs in Appendix 4 Table 7 were derived by micro-costing each health state. Some states with more serious complications required hospitalization. Some resource use was derived through clinical expert opinion.

Antiviral drug costs in Appendix 4 Table 8 include the manufacturer’s drug costs plus 10% pharmacy mark-up and a $7.00 pharmacist professional fee. Drug costs represent total prescription costs, and include patient and drug plan co-pay portions. Drug costs were incorporated into the model based on the cost of a one-week course of therapy, practice guidelines, and virological response rates.

In Appendix 4 Table 9, resource use for one course of AVT was based primarily on recommendations in the 2004 Canadian clinical practice guidelines. It includes physician visits, laboratory tests, liver biopsy, and HCV-RNA testing (qualitative and quantitative). Small out-of-pocket expenses were incurred by patients (for condoms, contraceptives, monthly pregnancy tests, and elective abortion) during AVT and 24 weeks after treatment because of the teratogenicity associated with RBV.

The analysis includes the costs of treating the adverse events that differed significantly between the two AVT strategies: serious infections and all other serious adverse events. Serious infections cost $151 and “all other serious adverse events” cost $173 (Appendix 4 Table 9). It was assumed that the
latter, which included a variety of serious adverse events, would require at least one emergency room visit each. This assumption was tested through a sensitivity analysis.

**Discounting:** Costs and health outcomes were discounted at an annual rate of 5%, with sensitivity analyses of 0% and 3%, as specified in the CADTH Guidelines.62

**Handling uncertainty and variability:** To assess the uncertainty and robustness of the base case results, one-way and multi-way deterministic sensitivity analyses were conducted for all key model parameters. Various methods were used to determine the parameter values for sensitivity analyses: confidence intervals related to sampling error, a plausible range of parameter values as determined by the literature or guidelines (e.g., the discount rate), and expert opinion or judgement where data were unavailable, for instance, to set a plausible range of values in Canada.

Variation in the population (e.g., mild CHC, mix of genotypes, age at start of AVT) and differences between jurisdictions or settings in Canada (regarding practice patterns, resource use, unit costs) were analyzed through a sensitivity analysis, so that the results are transferable to various Canadian jurisdictions.

**Software:** The model was built with the software program TreeAge Pro 2005 Suite (TreeAge Software Inc., Williamstown MA). The software program SAS 8 (SAS Institute Inc., Cary NC) was used for the statistical analyses of primary data.

c)  **Model validation**
Model validation comprised three levels. Technical validation involved checking the software program and cleaning it for potential programming bugs. Validation using different routine tests (e.g., setting SVR equal for all strategies, eliminating AVT costs, eliminating CHC-related mortality) yielded the expected results.

Internal validation involved comparing the model’s predictions with the data that was used. All data values were reproduced exactly by the decision model (e.g., SVR rates, progression incidences, background mortality).

External validation involved comparing the model’s predictions with published epidemiological data that were not used. The incidence of compensated liver cirrhosis developing in patients with mild CHC was adjusted for the spontaneous HCV remission rate of 31% in patients with acute HCV infection.66 The model predicted that 19% of patients with initial HCV infection would develop compensated liver cirrhosis over a 20-year period. This result is consistent with published data from prospective studies (i.e., 20%).67,68

Because the spontaneous HCV remission rate and the incidence of liver cirrhosis have been extracted from different sources, the use of different values for spontaneous HCV remission could lead to a proportional deviation from the cirrhosis incidence used in the validation. Different rates for spontaneous HCV remission would not influence the results from this model, because the target cohort of our analysis are patients with CHC.
5.2.2 Results

a) Base case

Health outcomes

Based on the SVR data from clinical trials, for every 1,000 patients treated, 453 and 607 patients would be expected to achieve an SVR when treated with IFN+RBV and PegIFN+RBV respectively. The model translated higher AVT-induced SVR rates into reduced risk for future liver complications and death.

<table>
<thead>
<tr>
<th>Table 7: Base case – health outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>SVR (6 months after end of treatment)</td>
</tr>
<tr>
<td>Compensated cirrhosis (from initially mild or moderate CHC)</td>
</tr>
<tr>
<td>Compensated cirrhosis (from initially mild CHC)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Liver transplantation</td>
</tr>
<tr>
<td>Liver death</td>
</tr>
</tbody>
</table>

AVT=antiviral therapy; CHC=chronic hepatitis C; IFN=interferon; LY=life-years; no AVT=no antiviral treatment; PegIFN=peginterferon; RBV=ribavirin; N/A=not applicable.

- Compared to no AVT, the model predicted that IFN+RBV would reduce the absolute risk of decompensated cirrhosis by 7.1%, hepatocellular carcinoma by 2.6%, liver transplant by 0.8%, and mortality due to liver failure by 7.1%.
- Compared to no AVT, PegIFN+RBV was predicted to reduce the absolute risk of decompensated cirrhosis by 9.6%, hepatocellular carcinoma by 3.5%, liver transplant by 1.1%, and mortality due to liver failure by 9.5%.

The relative reduction in the 20-year risk of liver disease and death is as follows:

- Compared to no AVT, the model predicted that IFN+RBV reduced the risk of decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and mortality due to liver failure by 33% to 36% in relative terms.
- Compared to no AVT, the model predicted that PegIFN+RBV reduced each of these outcomes by 45% to 49% in relative terms.

Over patients’ lifetimes:

- The model predicted that there would be 19 fewer liver transplants and 158 fewer deaths due to liver disease per 1,000 patients treated with IFN+RBV.
- With PegIFN+RBV, there would be 26 fewer liver transplants and 212 fewer deaths due to liver disease per 1,000 patients treated.

The undiscounted remaining life expectancy for the 43-year-old patient in the analysis was 28.5 years for no AVT, 31.4 years for IFN+RBV, and 32.4 years for PegIFN+RBV. The undiscounted remaining quality-adjusted life expectancy with the three strategies was 20.7 QALYs, 22.8 QALYs, and 23.5 QALYs respectively. Therefore, compared to no AVT, patients gained 2.9 LYs (2.1 QALYs) with IFN+RBV and 3.9 LYs (2.8 QALYs) with PegIFN+RBV.
The discounted remaining life expectancy for the 43-year-old patient in the analysis was 14.2 years for no AVT, 15.0 years for IFN+RBV, and 15.2 years for PegIFN+RBV. The discounted remaining quality-adjusted life expectancy with the three strategies was 10.3 QALYs, 10.8 QALYs, and 11.0 QALYs respectively.

**Costs**
The total undiscounted lifetime costs for each strategy are shown in Table 8.

### Table 8: Base case – disaggregated undiscounted lifetime costs ($)

<table>
<thead>
<tr>
<th>Undiscounted costs</th>
<th>Resources</th>
<th>No AVT*</th>
<th>IFN+RBV</th>
<th>PegIFN+RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral treatment</strong></td>
<td>Antiviral drugs</td>
<td>0</td>
<td>14,094</td>
<td>15,879</td>
</tr>
<tr>
<td></td>
<td>Treatment initiation</td>
<td>0</td>
<td>888</td>
<td>888</td>
</tr>
<tr>
<td></td>
<td>Office visits and laboratory**</td>
<td>0</td>
<td>1,268</td>
<td>1,423</td>
</tr>
<tr>
<td></td>
<td>Reproductive services</td>
<td>0</td>
<td>335</td>
<td>382</td>
</tr>
<tr>
<td></td>
<td>Harms†</td>
<td>0</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0</td>
<td>16,600</td>
<td>18,595</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of CHC-related complications</strong></td>
<td>Mild, moderate CHC, cirrhosis</td>
<td>10,321</td>
<td>5,756</td>
<td>4,199</td>
</tr>
<tr>
<td></td>
<td>Decompensated cirrhosis</td>
<td>8,809</td>
<td>5,559</td>
<td>4,451</td>
</tr>
<tr>
<td></td>
<td>Liver transplant</td>
<td>11,777</td>
<td>7,413</td>
<td>5,925</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30,907</td>
<td>18,728</td>
<td>14,575</td>
<td></td>
</tr>
<tr>
<td><strong>Lifetime costs</strong></td>
<td>30,907</td>
<td>35,328</td>
<td>33,170</td>
<td></td>
</tr>
</tbody>
</table>

* No treatment-associated costs assumed for no AVT; **including thyroid-stimulating hormone (TSH), polymerase chain reaction (PCR), other blood tests; † harms refers to costs associated with treating negative effects of AVT.

The total undiscounted lifetime cost of no AVT ($30,907) was less than the total cost of treatment with PegIFN+RBV ($33,170) and IFN+RBV ($35,328).

During the year of drug treatment, the PegIFN+RBV strategy cost $1,995 more than the IFN+RBV strategy ($18,595 versus $16,600). Initial treatment costs are higher because more patients treated with PegIFN+RBV show an early response to therapy and therefore continue treatment longer than those treated with IFN+RBV. This accounts for 90% of the higher cost; <1% of the difference was due to the higher cost of treating the harms associated with PegIFN+RBV.

In the longer term, PegIFN+RBV saved on outlays for treatment of CHC-related complications, and these costs were about half the level of the no AVT strategy. The savings were split between treatment of mild, moderate CHC, and cirrhosis (37%), decompensated cirrhosis (27%), and liver transplants (36%) when compared with IFN+RBV and no AVT.

On a discounted basis, the total lifetime cost of each of the two AVT strategies was approximately double that of no AVT. The total lifetime cost of treatment with PegIFN+RBV was less (by $2,161) than that of IFN+RBV, on an undiscounted basis, and more (by $270) than that of IFN+RBV on a discounted basis. The differences in the discounted and undiscounted results reflect differences in the timing of costs. The discounted costs of treating the CHC-related diseases 10 or 20 years in the future are 60% and 38% respectively of today’s undiscounted costs.

**Cost-effectiveness**
The results of the analysis are reported in terms of discounted incremental cost-effectiveness ratios (ICERs), which are reported as:
- incremental cost per life-year (LY) gained, and
incremental cost per quality-adjusted life-year (QALY) gained, formally known as incremental cost-utility ratios (ICUR).

The focus is on the results in terms of cost per QALY gained, rather than cost per LY gained, because the former measures the quantity and quality of life-years, and provides a better comparison with other health technologies. Some results are presented in terms of incremental cost per additional person with SVR. The expected lifetime costs and outcomes (i.e., SVR, LYs, and QALYs) of the strategies are reported in total and incremental terms (i.e., differences between the strategies). The discounted results (using the 5% discounted rate) are the focus for the discussion of cost-effectiveness.

When reporting ICERs, two terms are used here: strong dominance and weak or extended dominance. Strong dominance occurs when strategy A is both more effective and less costly than strategy B. Weak dominance occurs when strategy A is more effective and more costly, and has a lower ICER than strategy B. A two-step procedure is used to calculate ICERs: first, strongly dominated strategies are eliminated from the ICER calculation and ICER values are updated, then weakly dominated strategies are eliminated from the ICER calculation and ICER values are revised.

Table 9 shows the undiscounted and discounted expected lifetime costs, LY gained, QALYs gained, and SVR rates achieved; and the ICERs expressed as cost per SVR, cost per LY gained, and cost per QALY gained for each treatment strategy.

Table 9: Base case – undiscounted and discounted lifetime results

<table>
<thead>
<tr>
<th>Undiscounted</th>
<th>Cost ($)</th>
<th>Outcome</th>
<th>ICER</th>
<th>$/SVR</th>
<th>$/LY</th>
<th>$/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>no AVT</td>
<td>30,907</td>
<td>N/A</td>
<td>28.48</td>
<td>20.67</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IFN+RBV</td>
<td>35,329</td>
<td>0.453</td>
<td>31.39</td>
<td>22.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PegIFN+RBV*</td>
<td>33,168</td>
<td>0.607</td>
<td>32.39</td>
<td>23.51</td>
<td>3,725</td>
<td>578</td>
</tr>
<tr>
<td>Discounted at 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no AVT</td>
<td>12,819</td>
<td>N/A</td>
<td>14.22</td>
<td>10.33</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IFN+RBV</td>
<td>24,366</td>
<td>0.453</td>
<td>14.98</td>
<td>10.84</td>
<td>[25,497]</td>
<td>[15,110]</td>
</tr>
<tr>
<td>PegIFN+RBV*</td>
<td>24,636</td>
<td>0.607</td>
<td>15.24</td>
<td>11.03</td>
<td>19,464</td>
<td>11,532</td>
</tr>
</tbody>
</table>

*ICER versus next non-dominated strategy (no AVT). Numbers in parenthesis=weakly dominated strategy. AVT=antiviral therapy; ICER=incremental cost-effectiveness ratio; IFN=interferon alfa; LY=life-years; no AVT=no antiviral treatment; PegIFN=peginterferon alfa; QALY=quality-adjusted life-years; RBV=ribavirin; SVR=sustained virological response; N/A=not applicable.

The discounted ICER for PegIFN+RBV was $11,532 per LY gained and $16,969 per QALY gained compared to no AVT. In both situations, IFN+RBV was a weakly dominated strategy. The discounted cost per SVR is $19,464.

The base case results are plotted on the cost-effectiveness plane in Figure 2.
b) **Sensitivity analyses**

Sensitivity analyses were conducted to assess the uncertainty of the base case results. The discounted ICER results for PegIFN+RBV relating to changes in model parameter values appear in Tables 10 and 11. Appendix 4 Table 10 provides details about the discounted results of the three strategies. Undiscounted lifetime results appear in Appendix 4 Table 11.

The results reported as cost per LY gained are generally lower than those reported as cost per QALY gained, except sensitivity analysis 2a. For most sensitivity analyses, PegIFN+RBV weakly dominates IFN+RBV. Only for sensitivity analysis 10b (40% lower SVR rate for PegIFN+RBV) and sensitivity analysis 13b (conservative scenario) does IFN+RBV dominate PegIFN+RBV.

**Sensitivity analysis 1: patients with mild CHC only**

This sensitivity analysis was a model simulation and not based on clinical trial data from this subpopulation. The simulation was based on a cohort of patients with mild CHC only, rather than the base case cohort distribution of 52.3% mild CHC, 28.4% moderate CHC, and 19.3% compensated cirrhosis. The simulation uses the same SVR rates for patients with mild CHC as those used for the mixed base case population. Therefore, the results of this analysis may be a conservative estimate, because patients with mild CHC may have better treatment response rates than patients with more severe CHC. For example, Poynard et al.45 reported better treatment response rates for patients with no fibrosis or only portal fibrosis. A Cochrane review69 and a meta-analysis70 by Kjaergard et al. reported lower treatment response rates for patients with cirrhosis. Given these conditions, care should be taken when interpreting the results for this sensitivity analysis, especially the incremental cost per additional SVR.
Table 10: Sensitivity analysis – lifetime results discounted at 5%*

<table>
<thead>
<tr>
<th>Case</th>
<th>Sensitivity Analysis</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$/LY</td>
<td>$/QALY</td>
</tr>
<tr>
<td><strong>Base case</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. mild CHC patients only (base case: 52% mild CHC)</td>
<td>33,217</td>
<td>56,273</td>
</tr>
<tr>
<td>2a. genotype: 100% G2+3 (base case: 31%)</td>
<td>3,352</td>
<td>3,197</td>
</tr>
<tr>
<td>2b. genotype: 100% G non-2 G non-3 (base case: 69%)</td>
<td>18,476</td>
<td>28,767</td>
</tr>
<tr>
<td>3a. age 61 years at start of AVT (base case: age 43 years)</td>
<td>NC</td>
<td>49,600</td>
</tr>
<tr>
<td>3b. age 68 years at start of AVT</td>
<td>NC</td>
<td>99,200</td>
</tr>
<tr>
<td>Health states: low natural HCV disease progression rate (base case: 27.5% 20-year incidence of compensated cirrhosis for initially mild CHC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a. 4.6% 20-year incidence of compensated cirrhosis</td>
<td>NC</td>
<td>99,000</td>
</tr>
<tr>
<td>4b. 7% 20-year incidence of compensated cirrhosis</td>
<td>36,244</td>
<td>65,711</td>
</tr>
<tr>
<td>4c. 9.5% 20-year incidence of compensated cirrhosis</td>
<td>NC</td>
<td>48,900</td>
</tr>
<tr>
<td>4d. 20% 20-year incidence of compensated cirrhosis</td>
<td>NC</td>
<td>21,500</td>
</tr>
<tr>
<td>Health states: other probabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. higher % liver transplants: 4.9% decompensated cirrhosis and 4.9% hepatocellular carcinoma (base case: 3.3% and 0%)</td>
<td>10,892</td>
<td>16,038</td>
</tr>
<tr>
<td>6. no disease progression for viral negative patients (SVR) (base case: progression for moderate CHC and compensated cirrhosis)</td>
<td>8,350</td>
<td>12,013</td>
</tr>
<tr>
<td>Health states: utilities and costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7a. lifetime utility increment of 0.04 for viral negative patients (i.e., SVR) (base case: 0.04 utility increment for 1 year)</td>
<td>NC</td>
<td>11,100</td>
</tr>
<tr>
<td>7b. no utility increment for viral negative patients (i.e., SVR)</td>
<td>NC</td>
<td>17,600</td>
</tr>
<tr>
<td>8. health state utilities measured by EuroQoL instrument (base case: utilities measured by HUI instrument)</td>
<td>11,532</td>
<td>15,522</td>
</tr>
<tr>
<td>9a. 75% of annual treatment costs of CHC health states</td>
<td>13,186</td>
<td>19,402</td>
</tr>
<tr>
<td>9b. 150% of annual treatment costs of CHC health states</td>
<td>8,226</td>
<td>12,104</td>
</tr>
<tr>
<td>PegIFN+RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10a. 15% lower SVR rate for PegIFN+RBV</td>
<td>NC</td>
<td>21,600</td>
</tr>
<tr>
<td>10b. 40% lower SVR rate for PegIFN+RBV</td>
<td>NC</td>
<td>dominated†</td>
</tr>
<tr>
<td>11a. AVT adverse events: no cost and no utility reduction (base case: $151 and $173 depending on serious adverse event; 0.14 utility reduction)</td>
<td>11,510</td>
<td>14,862</td>
</tr>
<tr>
<td>11b. AVT adverse events: high cost and 0.20 utility reduction</td>
<td>11,570</td>
<td>18,107</td>
</tr>
<tr>
<td>12a. 20% PegIFN+RBV price increase</td>
<td>NC</td>
<td>22,000</td>
</tr>
<tr>
<td>12b. 59% PegIFN+RBV price increase</td>
<td>NC</td>
<td>50,000</td>
</tr>
<tr>
<td>Conservative scenarios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13a. 21% lower SVR rate for PegIFN+RBV and 25% lower health state costs</td>
<td>NC</td>
<td>49,400</td>
</tr>
<tr>
<td>13b. 25% lower SVR rate for PegIFN+RBV and 25% lower health state costs</td>
<td>NC</td>
<td>dominated†</td>
</tr>
</tbody>
</table>

*In sensitivity analyses 12b and 13a, ICER results for PegIFN+RBV calculated by comparison with IFN+RBV. In all other sensitivity analyses, ICER results for PegIFN+RBV calculated by comparison with no AVT, given that PegIFN+RBV weakly dominated IFN+RBV. †PegIFN+RBV dominated by IFN+RBV; AVT=antiviral therapy; CHC=chronic hepatitis C; HUI=health utilities index; IFN=interferon; LY=life-years; no AVT=no antiviral treatment; PegIFN=peginterferon; QALY=quality-adjusted life-years; RBV=ribavirin; SVR=sustained virological response; NC=not calculated.

Compared with no AVT, patients with mild CHC who are treated with PegIFN+RBV gained 0.5 LYs (0.3 QALYs) in the discounted analysis. Patients who are treated with IFN+RBV gained 0.3 LYs (0.2 QALYs) in the discounted analysis. The total discounted lifetime costs of no AVT for a 43-year-old patient with initially mild CHC was $6,238, compared with $21,112 for treatment with PegIFN+RBV and $20,067 for treatment with IFN+RBV.
In summary, patients with mild CHC treated with AVT had a higher ICER than a mixed population, as used for the base case. The cost per QALY for PegIFN+RBV versus no AVT was $56,273 compared to $16,969 in the base case. The result for IFN+RBV was $75,342 per QALY (Figure 3).

**Figure 3:** Cost-effectiveness plane – sensitivity analysis for patients with mild CHC (discounted lifetime costs and QALYs)

Sensitivity analyses 2a and 2b: variation in genotype mixture
In these sensitivity analyses, the proportion of patients with HCV genotypes other than 2 and 3 varied from 0% to 100% (Figure 4). The ICER for PegIFN+RBV was sensitive to the genotype mix in the population, varying from $3,200 per QALY for a cohort of G2+3 patients to $28,800 for a cohort of all other genotypes. For a cohort of G2+3 patients, PegIFN+RBV strongly dominated IFN+RBV (i.e., had better outcomes and lower lifetime costs).

Sensitivity analyses 3a and 3b: age at start of AVT
In Figure 5, the starting age for AVT varied from 20 years to 70 years (43 years is used in the base case). In the model, age is only reflected by changes in the background mortality rate (older patients are more likely than younger patients to die from a cause that is unrelated to CHC, given the slow natural progression of the disease). Age-specific natural progression or response to treatment is not considered in this analysis.

The ICER results are sensitive to this parameter and increase with the age at which AVT is started (Figure 5). Table 10 shows that the cost per QALY for PegIFN+RBV increases from $16,969 at age 43 years in the base case, to about $49,600 at age 61 years, and $99,200 at age 68 years.
Figure 4: Sensitivity analysis on proportion of patients with HCV genotypes other than 2 and 3

ICUR = incremental cost-utility ratio; IFN = interferon; PegIFN = peginterferon; RBV = ribavirin; no AVT = no antiviral treatment; QALY = quality-adjusted life-years.

Star represents ICER for base case: 69% with HCV genotypes other than 2 and 3.

Figure 5: Sensitivity analysis on age at start of antiviral treatment (20 to 70 years)

ICUR = incremental cost-utility ratio; IFN = interferon; PegIFN = peginterferon; RBV = ribavirin; no AVT = no antiviral treatment; QALY = quality-adjusted life-years.

Star represents ICER for base case: 43 years old at start of AVT.

Sensitivity analyses 4a to 4d: variation in natural progression rate of mild CHC

Sensitivity analyses were conducted on a range of natural progression rates expressed as the 20-year incidence of compensated cirrhosis. The quoted progression rates relate to the mild CHC cohort in the base case population, with the remainder of the base case population progressing faster to
cirrhosis. Table 10 shows that at a 20% progression rate, the ICER for PegIFN+RBV is $21,500 per QALY, compared with about $48,900 at a 9.5% rate, $65,711 at a 7% rate, and $99,000 at a 4.6% progression rate. The ICER increases steeply below a progression rate of about 15%. Figure 6 shows the results for the base case population when the natural progression rate for the mild CHC cohort varies from 4% to 40%.

The 7% progression rate was based on a meta-analysis of community-based studies, which included a large proportion (38%) of patients with normal ALT levels. Because normal ALT levels are associated with a reduced risk of developing cirrhosis, the 7% rate is conservative and would be an underestimation of the progression rate for the base case population, which consists of CHC patients with elevated ALT levels.

In summary, the cost per QALY increases as the progression rate of disease decreases; the slower the disease progression, the smaller the health gains realized from AVT, therefore, the higher cost per QALY.

**Figure 6: Sensitivity analysis on natural progression rate**

AVT=antiviral treatment; CHC=chronic hepatitis C; ICUR=incremental cost-utility ratio; IFN=interferon; PegIFN=peginterferon; RBV=ribavirin; no AVT=no antiviral treatment; QALY=quality-adjusted life-years. Star represents results for base case (Table 9)

**Sensitivity analysis 5: higher proportion of liver transplants**

In this sensitivity analysis, the annual proportion of patients with decompensated cirrhosis receiving a liver transplant increased from 3.3% in the base case to 4.9% (the upper CI as reported by Krahn). The annual proportion of patients with hepatocellular carcinoma receiving liver transplants was also set at 4.9% (compared to 0% in the base case).

Table 10 shows that the ICER for PegIFN+RBV decreased to $16,038 per QALY from $16,969 in the base case. Treatment with PegIFN+RBV reduced liver transplantation by 50% (36 cases per 1,000 CHC patients) compared with no AVT (71/1,000 CHC patients). IFN+RBV reduced liver transplants by 37% (44.5/1,000 CHC patients).
Sensitivity analysis 6: no disease progression for viral negative patients
In this sensitivity analysis, patients who are viral-negative (i.e., through spontaneous clearance or treatment SVR) did not progress to liver complications, contrary to the base case where patients with moderate CHC do progress in their disease (Appendix 4 Table 5). Table 10 shows that the ICER for PegIFN+RBV falls to $12,013 per QALY from $16,969 per QALY in the base case.

Sensitivity analyses 7a and 7b: utility increment for viral negative patients
In sensitivity analysis 7a, the 0.04 utility increment for achieving HCV negative status (occurring spontaneously or after AVT) is extended from one year in the base case to lifetime. The ICER for PegIFN+RBV decreased to $11,100 per QALY. When no utility increment for HCV negative status was used (sensitivity analysis 7b), the ICERs for PegIFN+RBV increased to $17,600 per QALY.

Sensitivity analysis 8: health state utilities measured by EuroQoL instrument
In this sensitivity analysis, the mean Health Utilities Index scores for the health states used in the base case were substituted with utilities based on the EuroQoL instrument (Appendix 4 Table 6). The ICER for PegIFN+RBV slightly changed from $16,969 per QALY in the base case to $15,522 per QALY.

Sensitivity analyses 9a and 9b: annual health state costs
In these sensitivity analyses, the annual base case costs of treating the CHC-related diseases (Appendix 4 Table 7) were multiplied by 75% and 150%, a range judged to represent the limits of variation of these costs in Canada.

Table 10 shows that the ICER of PegIFN+RBV was moderately sensitive to health state costs, increasing to $19,402/QALY at the 75% cost level and falling to $12,104/QALY at the 150% cost level.

Sensitivity analyses 10a and 10b: reduction in SVR rate for PegIFN+RBV
In Figure 7, the SVR rate for PegIFN+RBV was reduced by up to 40% of the base case rates. This analysis may be interpreted as mimicking a reduction in SVR, which may be attributed to various patient characteristics or to reduced compliance to therapy.

The ICER for PegIFN+RBV increased from $16,969 per QALY in the base case to $21,600 per QALY when the SVR rate was reduced by 15%, and to $35,600 per QALY when the SVR rate was reduced by 40%. IFN+RBV dominated PegIFN+RBV when the SVR was reduced by ≥19%.

In summary, a reduction in the SVR rate for PegIFN+RBV resulted in higher ICERs than in the base case (versus no AVT), but remained below $40,000 per QALY.

Sensitivity analyses 11a and 11b: cost and utility of AVT-related adverse events
- Sensitivity analysis 11a: no treatment-related utility reductions and no costs for the two adverse events (e.g., serious infections, all other rare serious adverse events) were associated with AVT. In this sensitivity analysis, the ICER for PegIFn+RBV decreased to $14,862 (versus $16,969 in the base case).
- Sensitivity analysis 11b: for this analysis, the utility reduction for AVT-related adverse events was increased to 0.20, and the cost of serious infections and all other rare serious adverse events (i.e., emergency room visits) were increased to $881 and $346 respectively. (Base case values were 0.14, $151 and $173 respectively). The ICER for PegIFn+RBV increased to $18,107 per QALY.
Figure 7: Sensitivity analysis on SVR rate for PegIFN+RBV

ICUR= incremental cost-utility ratio; IFN=interferon; PegIFN=peginterferon; RBV=ribavirin; no AVT=no antiviral treatment; QALY=quality-adjusted life-years

Sensitivity analyses 12a and 12b: price of PegIFN+RBV

Figure 8 shows how the ICERs vary when the price of PegIFN+RBV varies from 50% to 200% of its current price. At 120% of the current price, the ICERs for PegIFN+RBV and IFN+RBV were equal at about $22,000 per QALY. At this price, PegIFN+RBV no longer weakly dominates IFN+RBV. At 159% of the current price, the ICER of PegIFN+RBV, compared to IFN+RBV, increased to about $50,000 per QALY.

Sensitivity analyses 13a and 13b: Conservative scenarios

Very conservative scenarios, estimated by reducing annual treatment costs for cirrhosis and complications by 25% and reducing the SVR rate for PegIFN+RBV (Figure 9), were analyzed. In sensitivity analysis 13a, when the SVR was reduced by 21%, the ICER of PegIFN+RBV was about $50,000 per QALY compared with that of IFN+RBV. Higher SVR reductions resulted in higher ICERs for PegIFN+RBV. In sensitivity analysis 13b, PegIFN+RBV was strongly dominated by IFN+RBV when the SVR rates of PegIFN+RBV were reduced by ≥25%.

Sensitivity analysis 14: 3% annual discount rate

As suggested by CADTH’s economic guidelines, a sensitivity analysis was performed with costs and health outcomes discounted at a 3% rate. Table 11 shows that the ICER for PegIFN+RBV falls by half, to $7,900 per QALY, from $16,969 in the base case (using a 5% discount rate). IFN+RBV was dominated by PegIFN+RBV (i.e., PegIFN+RBV had lower lifetime costs and better outcomes).
Figure 8: Sensitivity analysis on price of PegIFN+RBV

![Graph showing sensitivity analysis on price of PegIFN+RBV](image)

ICUR= incremental cost-utility ratio; IFN=interferon; PegIFN=peginterferon; RBV=ribavirin; no AVT=no antiviral treatment; QALY=quality-adjusted life-years Star represents ICER for base case price of PegIFN+RBV.

Figure 9: Conservative scenario – lower annual costs for cirrhosis and complications, and lower SVR rate for PegIFN+RBV

![Graph showing conservative scenario](image)

ICUR=incremental cost-utility ratio; IFN=interferon; PegIFN=peginterferon; RBV=ribavirin; no AVT=no antiviral treatment; SVR=sustained virological response; QALY=quality-adjusted life-years
Table 11: Sensitivity analysis – annual discount rate of 3%

<table>
<thead>
<tr>
<th>Case</th>
<th>Cost ($)</th>
<th>Outcome</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incremental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cost-Effectiveness Ratio (ICER)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifetime Results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
</tr>
<tr>
<td>no AVT</td>
<td>17,400</td>
<td>N/A</td>
<td>18.09</td>
</tr>
<tr>
<td>IFN+RBV</td>
<td>27,200</td>
<td>0.453</td>
<td>19.34</td>
</tr>
<tr>
<td>PegIFN+RBV</td>
<td>26,800</td>
<td>0.607</td>
<td>19.76</td>
</tr>
</tbody>
</table>

*numbers rounded to nearest $100; ICER=incremental cost-effectiveness ratio; IFN=interferon; LY=life-years gained; no AVT=no antiviral treatment; PegIFN=peginterferon; QALY=quality-adjusted life-years gained; RBV=ribavirin; SVR=sustained virological response; N/A=not applicable.

6 HEALTH SERVICES IMPACT

6.1 Budget Impact

Budget impacts from the perspective of publicly funded drug plans and from that of clinics that treat patients who are infected with CHC were assessed. From the perspective of publicly funded drug plans in Canada that already pay for IFN+RBV, it was expected that PegIFN+RBV will replace IFN+RBV on a one-to-one basis should it also be covered by drug plans. If that happens, it was assumed that more CHC-infected individuals will likely seek treatment because of the higher SVR rates that result from PegIFN+RBV. In the base case, it was assumed that the number of patients treated increases by 10%.

Using the estimates in Table 8, the incremental cost to a drug plan of covering PegIFN would be about $337,000 per 100 patients currently treated with IFN+RBV (Table 12): PegIFN+RBV drug costs of $15,879 minus IFN+RBV drug costs of $14,094, multiplied by 100 patients, plus $15,879 multiplied by 10 to treat 10 more patients with PegIFN+RBV. In the sensitivity analysis, the estimate varies from $179,000 in the low case scenario (no increase in the treated population) to $496,000 in the high case scenario (20% increase in the treated population). Co-payments and deductibles are ignored in these calculations.

For a clinic that treats patients infected with CHC, additional costs for physician visits and laboratory work would amount to about $30,000 per 100 patients currently treated with IFN+RBV in the first year (Table 12): PegIFN+RBV regimen laboratory and visit costs of $1,423 minus IFN+RBV regimen laboratory and visit costs of $1,268 multiplied by 100 patients, plus $1,423 multiplied by 10 to treat 10 more patients with PegIFN+RBV. In the sensitivity analysis, the estimate varies from $16,000 in the low case scenario (no increase in the treated population) to $44,000 in the high case scenario (20% increase in the treated population). The estimates include only the marginal costs of treating patients and exclude the costs for hiring and training additional personnel or expanding facilities.

These calculations are based on the 2004 Canadian Consensus guidelines and ignore the long-term cost offsets of treating fewer patients with CHC-related long-term liver diseases. If successful treatment reduces the population infected with HCV, it also potentially reduces the transmission of the virus to other people, thereby providing another benefit.
### Table 12: Cost assessment of funding PegIFN+RBV in place of IFN+RBV

<table>
<thead>
<tr>
<th></th>
<th>PegIFN+RBV</th>
<th>IFN+RBV</th>
<th>Per Patient</th>
<th>Per 100 Patients (Low Case)</th>
<th>10% Increase* (Base Case)</th>
<th>20% Increase* (High Case)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug costs</strong></td>
<td>$15,879</td>
<td>$14,094</td>
<td>$1,785</td>
<td>$178,500</td>
<td>$337,290</td>
<td>$496,080</td>
</tr>
<tr>
<td><strong>Office visits and laboratory tests</strong></td>
<td>$1,423</td>
<td>$1,268</td>
<td>$155</td>
<td>$15,500</td>
<td>$29,730</td>
<td>$43,960</td>
</tr>
</tbody>
</table>

* assumes that 10 or 20 additional patients treated with PegIFN+RBV for every 100 cases previously treated with IFN+RBV

IFN=interferon; PegIFN=peginterferon; RBV=ribavirin.

### 6.2 Planning, Implementation, and Ethical Issues

The management of CHC will evolve as the understanding of the disease and its treatment advances. Research is underway to develop therapies; it may be five years before any of these treatments reach the market. Some of the drugs under investigation include oral protease or polymerase inhibitors, immunomodulators, new types or formulations of IFN, and alternatives to RBV. In the short term, IFN-based therapies will likely remain the mainstay of treatment. As new information becomes available, the dose and duration of PegIFN-based combination therapies will likely be modified for the various subpopulations.

Adherence to treatment (unreduced dosage, frequency of administration, and persistence through the course of treatment) is a factor in determining whether patients achieve SVR. Data on real-world adherence in Canada are unavailable, although literature from the BC Ministry of Health suggests that in demonstration projects where treatment adherence is monitored by nurses, 50% of patients achieve a SVR. This is similar to the rate found in clinical trials. Similar nurse support programs exist throughout Canada and may enhance therapy adherence.

A modest increase (of perhaps 10%) in the number of patients with CHC who are treated with PegIFN+RBV is projected based on the improved SVR rates compared with IFN+RBV. Therefore, additional human and financial resources will be required to handle this increase.

This report’s sensitivity analysis showed that the ICER results are sensitive to the patient’s age at the start of treatment, and that above an age of about 61 years, the cost per QALY increases to >$50,000. This factor can be considered by decision makers who use cost-per-QALY thresholds when making funding and treatment decisions.

This report does not address the impact of treating subgroups of patients such as those with HIV or hepatitis B co-infection, treatment relapsers, or non-responders, because of the lack of data and the modelling complexities.

### 7 DISCUSSION

#### 7.1 Summary of Results

This analysis was conducted using a validated decision-analytic model that had been used for previous cost-effectiveness analyses of antiviral treatments for CHC. The model was modified to
align it with Canadian clinical practice guidelines, and available Canadian data were used to populate the model. The population in the model had an average age of 43 years, had CHC, and was treatment-naïve with elevated ALT levels. Three strategies were evaluated: no AVT, treatment with IFN+RBV according to the 2000 Canadian clinical practice guidelines, and treatment with PegIFN+RBV according to the 2004 Canadian clinical practice guidelines (including the 12-week testing and stopping rule). Statistically significant serious adverse events from treatment were included in the analysis. The perspective was that of the Canadian publicly funded health care payer. Effects and costs were discounted annually by 5%. Reported outcomes were undiscounted LYs gained, QALYs gained, 20-year risk of CHC-related liver complications, and discounted incremental cost-effectiveness ratios (cost per LY and cost per QALY gained).

SVR rates from treatment were extrapolated to relevant long-term health outcomes. Based on an analysis of clinical trial data, it was found that:

- PegIFN+RBV was associated with a higher SVR rate than IFN+RBV. If data from clinical trials are applied to the Canadian genotype mix, the overall SVR rate for PegIFN+RBV was estimated to be 61% versus 45% with IFN+RBV
- patients infected with genotype 2+3 have higher SVR rates than those infected with other genotypes
- PegIFN+RBV was associated with a significantly higher rate of non-fatal serious adverse events (rate ratio 1.24, 95%CI: 1.01 to 1.51)
- no significant difference was detected between PegIFN+RBV and IFN+RBV in withdrawals due to adverse events.

7.1.1 Base Case results

a) Over patients’ lifetimes:
- the model predicted that there would be 19 fewer liver transplants and 158 fewer deaths due to liver disease per 1,000 patients treated with IFN+RBV, when compared to no AVT
- with PegIFN+RBV, there would be 26 fewer liver transplants and 212 fewer deaths due to liver disease per 1,000 patients treated, when compared to no AVT.

b) Treatment with PegIFN+RBV improved health outcomes compared with IFN+RBV:
- 1.0 LYs gained and 0.7 QALYs gained, on an undiscounted basis (0.3 and 0.2 respectively, when discounted at a 5% rate)
- PegIFN+RBV reduced the 20-year absolute risk of decompensated cirrhosis by 2.5%, hepatocellular carcinoma by 0.9%, and liver transplant by 0.3%
- CHC-related deaths were reduced from 13% to 10.6% over 20 years, and over patients’ lifetimes, there were an estimated 54 fewer deaths per 1,000 patients treated.

c) Treatment with PegIFN+RBV improved health outcomes compared with no AVT:
- 3.9 LYs gained and 2.8 QALYs gained, on an undiscounted basis (1.0 and 0.7 respectively, when discounted at a 5% rate);
- the absolute 20-year risk of decompensated cirrhosis was reduced by 9.6%, hepatocellular carcinoma by 3.5%, and liver transplant by 1.1%
- CHC-related deaths decreased from 20.1% of the cohort to 10.6%, with treatment.
d) In terms of costs, treatment with PegIFN+RBV:

- was not cost-saving when evaluated over patients’ lifetimes (i.e., total lifetime costs using PegIFN+RBV were more than the total lifetime cost with no AVT)
- reduced the long-term costs of treating CHC-related complications compared with IFN+RBV and no AVT
- was more costly ($24,636 versus $24,366) than IFN+RBV in terms of total discounted lifetime costs; and
- was more costly than IFN+RBV ($16,600 versus $18,600) during the year of drug treatment, mainly because more patients treated with PegIFN+RBV showed an early response to therapy and therefore continued treatment longer than those treated with IFN+RBV.

The cost per patient of treating harms associated with AVT was higher for PegIFN+RBV compared with IFN+RBV ($23 versus $15). The cost of treating harms due to either AVT regimen, relative to no AVT, was not calculated.

e) The ICERs for PegIFN+RBV compared with no AVT (the non-dominated strategy) were:

- $17,000 per QALY gained
- $11,500 per LY gained
- $19,500 per additional SVR.

There is no accepted standard in Canada regarding what constitutes “good value for money” in the adoption of health technologies. The results of the analysis fall within the range of cost-per-QALY results (based on 2002 US dollars) for selected health technologies reported in an article by Neumann et al.:76

- $10,000 to $25,000 for screening (mammography, colon cancer, and osteoporosis)
- $10,000 to $60,000 for anti-hypertensive medication (in patients with diastolic blood pressure >105 mm Hg)
- $10,000 to $50,000 for cholesterol management as secondary prevention
- $30,000 to $85,000 for implantable cardioverter-defibrillator
- $50,000 to $100,000 for dialysis in end-stage renal disease.

f) Results of Sensitivity Analyses

- The cost per QALY results were robust in most of the sensitivity analyses performed, with some exceptions.
- PegIFN+RBV was more effective and had a lower ICER than IFN+RBV in most of the sensitivity analyses performed.
- In the sensitivity analysis that simulated treatment of mild CHC patients, the ICER for PegIFN+RBV was higher than in the base case ($56,000 per QALY versus $17,000 per QALY). This is a conservative estimate, and care should be taken when interpreting this result because patients with mild CHC may have better treatment response rates than those used.
- Treating patients who have genotypes 2 and 3 with PegIFN+RBV was associated with lower ICERs than treating patients with other genotypes ($3,200 per QALY versus $28,800 per QALY), because the former showed a higher SVR rate to AVT and is therefore assumed to have better long-term outcomes.
• When the SVR for PegIFN+RBV was reduced by 40%, the ICER increased to about $36,000 per QALY compared to no AVT. At a 19% reduction, IFN+RBV costs less and is more effective than PegIFN+RBV (i.e., IFN+RBV strongly dominated PegIFN+RBV).
• The conservative scenario combining unfavourable health states costs with a 21% lower SVR rate for PegIFN+RBV resulted in an ICER of about $50,000 per QALY compared to IFN+RBV.

The ICER results for PegIFN+RBV were most sensitive to two model parameters (the disease progression rate and the age at the start of treatment).
• Lower rates of natural disease progression increased the cost per QALY of PegIFN+RBV. Patients whose disease progresses more slowly have smaller health gains from AVT, with lower costs for treating CHC-related complications because they have fewer of them in their lifetime. Compared with no AVT, when the 20-year incidence of cirrhosis was lowered from the base case incidence (27.5% to 20%), the cost per QALY increased to about $21,500. At a 7% rate, the ICER for PegIFN+RBV increased to about $65,700 per QALY, and at 4.6%, it was $99,000 per QALY. The 7% and 4.6% rates are conservative and would be expected to be an underestimate of the progression rate for the base case population.
• The ICER results increase with the age at which treatment is started. The cost per QALY for PegIFN+RBV increases from $17,000 at age 43 in the base case, to about $50,000 at age 61, and $100,000 at age 68. This reflects the fact that patients are more likely to die from other causes before developing serious liver disease.

7.2 Study Limitations

Most of the limitations in this study relate to the lack of data for the model parameters.
• The rate of natural progression of CHC disease varies in published epidemiologic studies. There is also a lack of reliable data on the rate of progression for patients with different characteristics. The rates depend on the study design, population, and the impact of possible biases. In a review of 57 studies on the natural history of hepatitis C, the authors classified the studies into four categories of study design and used regression analysis to derive the pooled progression estimates for each category. The estimated 20-year risk of cirrhosis was 24% for post-transfusion cohorts, 22% for liver clinic series, 7% for community-based cohorts, and 4% for blood donors. Adjusting for demographic and clinical characteristics explained a small part of the heterogeneity. It has been argued that biases such as referral bias and selection bias may explain the high cirrhosis risks in liver series and post-transfusion cohorts, and the low estimates in blood donors. The percentage of patients with elevated ALT levels varied in the different settings and was as low as 62% in the community-based studies. The sensitivity of the ICER results was assessed using a lower rate of progression that biases the analysis against the AVT strategies.
• The correlation between SVR rates and improved long-term health outcomes (reduced CHC-related complications and mortality) requires follow-up that occurs beyond what is considered to be feasible in a RCT. Information on the long-term benefits of AVT is evolving as treated cohorts are examined in epidemiologic studies.
• Genotype-specific virological response data available from the clinical trials did not permit confidence intervals to be estimated for the SVR rates of the two AVT strategies. The sensitivity of the results to this model parameter was assessed by reducing the SVR rate for PegIFN+RBV by up to 40%.
• The cost-effectiveness estimates for using AVT to treat patients with mild CHC are conservative and should be interpreted with caution given the lack of specific treatment data for this population.
• In the clinical trials, an elevated ALT level was used as a marker for more severe CHC disease and as a criterion for treatment. In Canadian clinical practice, the extent of liver fibrosis – not ALT levels – is the suggested marker that is used to determine CHC disease severity. Some patients with normal ALT levels have significant fibrosis and require treatment. The impact that this factor has on the outcomes of the clinical trials is unknown.

• The model accounted for a proportion of patients dying of CHC-related liver disease and liver transplantation, and assumed that those who died of other causes would have the same death rate as the Canadian general population with the same age and sex. This assumption was made partly because accurate Canadian epidemiological data were limited regarding the mortality of hepatitis C patients, cause-specific death rates, and how these death rates compare with those of the general population. General population all-cause mortality rates have been used in other analyses, and there is limited evidence to suggest that cases with hepatitis C may have similar all-cause death rates (excluding liver disease-related death) as the general population. While patients with CHC often have other risk factors or comorbidities that may make them more likely to die sooner than the general population (e.g., IV drug use, HIV infection, alcohol abuse, conditions that require blood transfusion), data included in this model were obtained from patients who were free of HIV and other comorbid conditions, as stated in the trial exclusion criteria. The use of these data may bias the results in favour of treatment, with this potential bias being less of a concern between treatments.

• As in many decision-analytic models, we had to simplify, so cohorts were modelled using average transition probabilities. There are no sufficiently robust data to create a micro-model based on patient characteristics. However, SVR rates and progression rates may depend on individual patient characteristics. Using average transition probabilities rather than subgroup-specific parameters may bias the model results in favour of treatment for some subgroups. In some cases, patient characteristics that favour treatment response (i.e., SVR) may be associated with a reduced risk of developing cirrhosis. Thus, it is more likely that non-responders have a more severe natural history, on average, than untreated people (who may or may not respond). To address this variability in response, we performed a sensitivity analysis with low values for progression (sensitivity analyses 4a, b, c, and d) in all patients, which included those with a sustained response; and an analysis where SVR was reduced by up to 40% of the base case (sensitivity analyses 10a and b).

• The report does not provide specific evidence of adherence in the real world, or the impact of reduced adherence on SVR. These data are limited. Although it is reasonable to expect that adherence will be lower in the real world than in trials, and that lack of adherence would result in lower efficacy, there is evidence to suggest that the safety and efficacy of PegIFN+RBV in clinical practice are comparable with the results of RCTs. Our report conducted sensitivity analyses with reduced SVR (i.e., sensitivity analyses 10a and b) for PegIFN+RBV. These sensitivity analyses can be interpreted as mimicking a lower adherence than that in the clinical trials. Similarly, other levels of therapeutic adherence can be interpreted from Figure 7.

• The model does not address other interventions that occur in the real world, such as alcohol abstinence or weight loss. While these are important in the clinical management of CHC and could be cost-effective, their evaluation was excluded from the objectives of this analysis.

• The costs of treatment-related adverse events were included in the model only where serious adverse events were significantly different between the two treatment regimens. Any differences in adverse events between AVT and no AVT (i.e., placebo) were excluded from the model. However, the disutility of treatment-related adverse events versus no AVT was included. The impact of adverse events was further tested in sensitivity analysis 11b (increased utility reduction and adverse event treatment costs).
• A possible benefit from successful treatment could be a reduction in the population infected with HCV, thereby potentially reducing the transmission of the virus to uninfected individuals. However, quantifying this is beyond this project’s scope.
• There are no available data on how many patients receive biopsies before AVT, and so it was assumed in this analysis that all patients receiving AVT would have one. Given the relative cost of biopsies, the impact on the results is likely to be small, biasing the estimate against AVT.
• The model results do not address the impact of treating subgroups of patients such as those with HIV or hepatitis B co-infection, relapers, or non-responders. Because of the lack of data and the modelling complexities, these populations were not addressed in this report.
• A probabilistic sensitivity analysis may have provided less parameter uncertainty, and given that probabilistic sensitivity analysis is becoming a standard approach, this may be viewed as a study limitation. A probabilistic analysis is based on knowledge about the joint distribution of the parameters in the model. This knowledge is limited for hepatitis C, so future research should be conducted with the aim of improving our knowledge and estimates. The use of the deterministic approach to the sensitivity analysis in this study enabled an assessment of how the model’s results were affected by changing assumptions about genotype, disease progression, and costs. The authors of this study believe that the sensitivity analysis presented here is valid and of a high quality, however, the lack of a probabilistic sensitivity analysis may be seen as a study limitation.

7.3 Generalizability of Findings

The findings of the economic evaluation can be considered to be generalizable to the jurisdictions in Canada when the sensitivity analyses are taken into account. Canadian data on epidemiology, resource use, unit costs, and clinical practice (based on the 2004 Canadian Consensus guidelines) were used in the model, and a plausible range of parameter values expected to be relevant to Canada were tested in the sensitivity analysis. This analysis is relevant to the population described in the model (i.e., treatment-naïve patients with CHC who are identified through routine care and who have elevated ALT levels and limited co-morbidities). Subgroups (e.g., genotype, patients with mild CHC, age at start of treatment) were simulated, and natural disease progression was subject to an extensive sensitivity analysis, subject to the limitations noted in section 7.5.

7.3.1 Findings of Other Economic Studies

Nine economic evaluations were found that analyzed the cost-effectiveness of PegIFN+RBV compared with IFN+RBV for treatment-naïve patients with CHC. This systematic review found the following:
• All nine studies, including the three independently sponsored studies, concluded that, on average, PegIFN+RBV was a cost-effective treatment for patients with CHC compared with IFN+RBV.
• The results of the sensitivity and subgroup analyses were robust (i.e., less than the cost-effectiveness threshold assumed in the particular study) in all the cases analyzed in five studies.
• In the other four studies, results of sensitivity and subgroup analyses were generally cost-effective, with the following exceptions:
  (i) two studies analyzed low natural rates of progression (20-year risk of cirrhosis of 9% to 10%)
  (ii) one of these studies focused exclusively on patients with mild CHC, using lower progression rates than in other studies; this study found that the ICER results varied depending on gender (higher for females), genotype (higher for G1 versus G2+3) and utility assumptions; the results were not cost-effective for females with G1 because of the lower progression rate.
• Four of five studies that analyzed the cost-effectiveness of treating different genotypes found that the ICER results for treating G non-2+3 with PegIFN+RBV were higher than for G2+3.
• Two studies found the 12-week stopping rule to be cost-effective when treating G non-2+3 with PegIFN+RBV.
• Results were sensitive to the utility of health states, SVR, or treatment-related adverse events in two studies. (This was not the case in our study.)
• When generalizing the results to Canada, the price of a full course of PegIFN+RBV in all nine studies was greater than that of a full course of IFN+RBV. Therefore, better ICER results would be expected for PegIFN+RBV if the two AVT strategies were priced equally (as they are in Canada). On the other hand, all the studies used a lower discount rate than the 5% rate used for the base case in this study. The net impact of these two counteracting factors on the ICER results is uncertain.

7.4 Health Services Impact

Drug plan coverage of PegIFN+RBV is expected to result in a modest increase (perhaps 10%) in the number of CHC patients who are treated with PegIFN+RBV because of the improved SVR rates compared with IFN+RBV. The impact on publicly funded drug plan budgets and HCV clinics is expected to be modest, although in the latter case, additional human and financial resources may be required. This may exacerbate the current shortage of physicians working in this area.

The likelihood of adherence with treatment is a factor for physicians to consider when deciding whether to treat patients with CHC. Reports from some CHC treatment programs indicate that support and monitoring of patients by nurses are likely to improve treatment adherence and thereby improve SVR.

A decision to treat patients must take into account factors such as the patient’s health status (related to CHC infection or other comorbidities), risk of liver disease progression, likelihood of treatment response, risk of adverse effects, symptoms, and view of treatment. The sensitivity analysis in this report indicates that the cost-effectiveness of treatment with PegIFN+RBV is sensitive to the age at initiation of treatment, and that above an age of about 61 years, the cost per QALY increases to >$50,000. This factor can be considered by decision makers who use cost-per-QALY thresholds when making funding and treatment decisions.

7.5 Knowledge Gaps

There are knowledge gaps about CHC, the factors affecting a patient’s prognosis, and the effect of treatment on disease progression. No head-to-head clinical trials of pegylated interferon alfa-2b plus RBV (Pegetron™) and pegylated interferon alfa-2a plus RBV (Pegasys RBV®) were found, so there is no evidence to suggest whether one product is superior to the other in SVR or health outcomes. The lack of clinical trial data for patients who were following the various management strategies limited our ability to conduct a comparative analysis of treatment-stopping rules. Filling these knowledge gaps will provide more reliable clinical and economic information to determine how patients should be identified and treated.

This report does not address the impact of treatment on other patient subgroups, such as treatment relapers and non-responders, those with co-morbidities (such as HIV or hepatitis B co-infection), and those with HCV risk factors, such as injection drug use and incarceration. Further analysis of additional data on these patients would assist those making funding and clinical treatment decisions.
8 CONCLUSIONS

An economic evaluation was undertaken, from a Canadian public payer perspective, of treating CHC-infected adults in Canada using a combination of PegIFN and RBV compared with standard IFN and RBV, and no AVT.

In the base case analysis, the model predicted that PegIFN+RBV treatment improves health outcomes for the average patient compared with no AVT: 1.0 discounted LYs gained; 0.7 discounted QALYs gained; a reduction in the 20-year risk of CHC-related liver complications by 45% to 60%; and a reduction in the 20-year risk of CHC-related deaths from 20.1% to 10.6%. Treatment with PegIFN+RBV also improved health outcomes compared with IFN+RBV.

PegIFN+RBV weakly dominated IFN+RBV in the base case and in most of the sensitivity analyses. The results for PegIFN+RBV were most sensitive to two model parameters: the natural disease progression rate and the age at the start of treatment.

Treatment with PegIFN+RBV was not cost saving when evaluated over patients’ lifetimes. Treatment with PegIFN+RBV is expected to increase drug budgets that already fund IFN+RBV. The total discounted lifetime cost of treatment with the two regimens is about the same, given the lower costs of CHC-related complications for patients treated with PegIFN+RBV.

The findings of this report are consistent with those of the nine economic evaluations identified in this systematic review of the published literature. All nine studies reported that, on average, PegIFN+RBV was associated with better outcomes and higher costs for patients with CHC when compared to IFN+RBV.
9 REFERENCES


APPENDICES

Available from CADTH’s web site
www.cadth.ca