CADTH

CADTH THERAPEUTIC REVIEW

Drugs for Chronic Hepatitis C Infection: Recommendations Report

Product Line:	Therapeutic Review
Version:	1.0
Volume Number:	3
Issue Number:	1d
Publication Date:	June 2016
Report Length:	33

This report was originally published in November 2015. In June 2016, minor changes were made to descriptions of the results for genotype 1b infection on pp. 14, 16 and 17. These changes are described in detail in the Record of Amendments.

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

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Views: CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

Cite as: Drugs for chronic hepatitis C infection: recommendations report. Ottawa: CADTH; 2015 Nov. (CADTH therapeutic review; vol.3, no.1d).

Contact **requests@cadth.ca** with inquiries about this notice or legal matters relating to CADTH services.

ISSN: 1929-7440

Acknowledgements

CADTH would like to thank the following organizations that responded to calls for stakeholder feedback on this Therapeutic Review. This feedback was carefully considered by CADTH and the CADTH Canadian Drug Expert Committee.

- AbbVie
- Action Hepatitis Canada
- Bristol-Myers Squibb Canada
- Canadian Liver Foundation
- Canadian Treatment Action Council
- Correctional Service Canada
- Gilead Sciences Canada, Inc.
- HepCBC Hepatitis C Education and Prevention Society
- Janssen Inc.
- Merck Canada
- Ministry of Health — Province of British Columbia
- Non-Insured Health Benefits Directorate, First Nations & Inuit Health Branch, Health Canada / Government of Canada
- Ontario Public Drug Programs, Ministry of Health and Long-Term Care

Table of Contents

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	CADTH Canadian Drug Expert Committee
NMA	network meta-analysis
QALY	quality-adjusted life-year
RCT	randomized controlled trial

Background

According to estimates from 2007, approximately 242,000 Canadians are chronically infected with hepatitis C virus (HCV) and the number may grow by 7,900 new infections each year.[1] Prevalence and incidence may be underestimated, as 30% to 70% of patients are unaware that they are infected.[2] Studies have reported that 15% to 25% of patients with chronic hepatitis C (CHC) infection develop hepatocellular carcinoma or progressive liver disease within 20 years of infection, resulting in liver transplantation for some, and decreased life expectancy and quality of life for many. However, the lifetime risk of developing complications of CHC infection may be higher depending on the duration of infection and the profile of competing risk factors over time.[3,4] HCV can be divided into several unique genotypes, each with one or more subtypes. Genotype 1 is the most common in Canada (55% to 65%) and historically the most difficult to cure.[5,6] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively. Genotypes 4, 5, and 6 are less common in Canada and account for less than 5% of HCV cases.[6,7] The goal of therapy for patients with CHC infection is to achieve sustained virologic response (SVR); i.e., undetectable HCV at 12 or 24 weeks after completion of anti-HCV treatment. The vast majority of patients who achieve SVR remain free of detectable HCV over the long term (unless reinfected); hence, SVR is considered to represent virologic cure. Treatment of CHC infection is guided by genotype, the presence and degree of liver fibrosis or cirrhosis, prior treatment experience, and patient factors such as the presence of comorbidities.

Until 2011, treatment for CHC infection consisted of pegylated interferon (PEG-IFN) plus ribavirin (PR). Following regulatory approvals beginning in 2011, direct-acting antiviral agents (DAAs) became available, including protease inhibitors (boceprevir [BOC], telaprevir [TEL], simeprevir [SIM]) for use in combination with PR for genotype 1 infection, and a nucleotide polymerase inhibitor (sofosbuvir [SOF]) for use in combination with PR for genotypes 1 and 4, and in combination with ribavirin (RBV) for genotypes 2 and 3. Treatment choices have since increased to include interferon-free regimens; as a result, the 2014 CADTH Therapeutic Review that evaluated the clinical and cost-effectiveness of the above-listed DAAs with PR for treatment of CHC genotype 1 infection has been updated to include these newer regimens, and to expand the analysis to genotypes 1 through 6. Three interferon-free therapies have been approved by Health Canada since the 2014 Therapeutic Review: ledipasvir (LDV) combined with sofosbuvir (Harvoni); dasabuvir (DAS), ombitasvir (OMB), and paritaprevir/ritonavir (PAR/RIT) (Holkira Pak); and daclatasvir (DCV) (Daklinza) combined with sofosbuvir. Apart from these regimens, the updated review also considered a number of emerging regimens.

Policy Questions

Evidence-informed recommendations were developed by the CADTH Canadian Drug Expert Committee (CDEC) to address the following policy questions:

1. How should interferon-free DAA regimens be listed for reimbursement for CHC infection (genotypes 1 to 6)?
2. Should reimbursement of regimens for CHC infection be guided by fibrosis staging and limited to fibrosis stages ≥ F2?
3. Should re-treatment with a DAA regimen be reimbursed for patients with CHC infection who fail to achieve SVR on another DAA regimen?

Preamble to the Recommendations

The treatment strategies for CHC infection have continued to evolve rapidly since CADTH's 2014 Therapeutic Review of this area. As anticipated by CDEC in its recommendations at the time, all-oral regimens that do not include interferon and others that also do not include ribavirin have been approved for use in Canada. Compared with interferon-based regimens, these new regimens are anticipated to offer higher cure rates and safety benefits in addition to the shorter treatment durations desired by patients. These regimens are also associated with high costs. Due to the relatively high prevalence of CHC infection and the likely increase in demand for treatment with the introduction of more effective, better-tolerated, all-oral therapies, the newer regimens for CHC infection have the potential to significantly affect health system sustainability. To address the needs of policy-makers related to this complex and dynamic clinical area, CADTH has updated and expanded its Therapeutic Review of treatments for CHC infection, and CDEC has revised its recommendations based on the updated review.

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the therapies compared with each other, along with patient group input, were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that the budget impact of treatments for CHC infection can be very large; therefore, health system sustainability was also considered in developing recommendations.

The evidence for developing CDEC recommendations was derived from the following reports:

1. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review. Drugs for Chronic Hepatitis C Infection — Clinical Review [Internet]. Ottawa: The Agency;[8]
2. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review. Drugs for Chronic Hepatitis C Infection — Cost-Effectiveness Analysis [Internet]. Ottawa: The Agency;[9]
3. Patient Input to CADTH Therapeutic Review: Drugs for Chronic Hepatitis C Infection [Internet]. Ottawa: The Agency.[10]

A challenging aspect of the evidence base for newer regimens for CHC infection is that nearly all studies are either uncontrolled or have employed only historical controls. The Committee recognized that there may have been ethical or logistical challenges that necessitated such designs, and that they have been accepted for regulatory approval. However, the lack of appropriately controlled trials causes difficulties in assessing comparative efficacy, safety, and cost-effectiveness. While methods for synthesizing evidence from single-arm trials in indirect treatment comparisons (IDCs) are emerging, the Committee considered analyses employing these methods to be associated with greater uncertainty compared with IDCs based on controlled trials.

Treatment of CHC infection is a dynamic therapeutic area. Several regimens not yet approved in Canada have been studied in trials and CADTH's systematic review captured the available evidence for a number of these regimens. While the Committee made formal recommendations only on approved regimens, it also noted instances in which unapproved regimens recommended by the Canadian Association for the Study of the Liver (CASL) guidelines[11] appeared favourable with respect to efficacy, safety, or cost-effectiveness.

CDEC noted that all patients with CHC infection should be treated only by clinicians who have expertise and experience in treating patients with this condition.

CADTH Canadian Drug Expert Committee Values and Preferences

CDEC sought to balance patients' reported needs and perspectives, clinical evidence, and economic evidence. The Committee considered efficacy, safety, cost-effectiveness, and patient preferences to be particularly important in making these recommendations.

In considering patient perspectives, CDEC noted patients' desire for the most effective treatment, for faster and surer access to treatment for individuals with less-advanced disease, and for more nuanced criteria for assessing individuals' eligibility for treatment and their clear preference for DAAs with shorter treatment durations and less toxicity.

CDEC considered the high costs of newly available treatments, the likely impacts of these costs on other parts of the public health care system, and the rapid evolution of CHC therapy to be important when drafting the recommendations.

CDEC noted that patients with CHC infection should be treated and monitored by physicians with experience in the management of the condition.

Summary of Recommendations

Recommendation 1:

CDEC recommends that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.

Recommendation 2:

CDEC recommends ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin as preferred regimens for treatment-naive and peginterferon plus ribavirin (PR)-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status. The recommended duration of therapy is as per the Health Canada–approved monograph for each regimen.

Conditions:

Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Recommendation 3:

CDEC recommends the following as preferred regimens for patients with CHC infection genotypes 2 through 4:

- Genotype 2: sofosbuvir/ribavirin for 12 weeks
- Genotype 3, without cirrhosis: daclatasvir/sofosbuvir for 12 weeks
- Genotype 3, with cirrhosis: sofosbuvir/ribavirin for 24 weeks
- Genotype 4, treatment-naive without cirrhosis: sofosbuvir/pegylated interferon/ribavirin for 12 weeks
- Genotype 4, treatment-experienced or with cirrhosis regardless of treatment experience: insufficient evidence to make a recommendation.

Conditions:

Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Recommendation 4:

CDEC considered there to be insufficient evidence to make a recommendation for patients with CHC genotype 5 or 6 infection.

Recommendation 5:

CDEC recommends ledipasvir/sofosbuvir as the preferred regimen for patients with genotype 1 infection previously treated with a protease inhibitor-peginterferon/ribavirin regimen, regardless of cirrhosis status. CDEC considered there to be insufficient evidence to make a recommendation for patients previously treated with an all-oral DAA regimen.

CDEC considered there to be insufficient evidence to make a recommendation for patients with non-genotype 1 CHC infection previously treated with a DAA-based regimen.

Conditions:

Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Recommendations

Recommendation 1

CDEC recommends that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.

Reasons for Recommendation 1

- Based on the CADTH cost-effectiveness analysis, CDEC considered treatment of CHC infection was likely cost-effective across all Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scores based on generally accepted thresholds. However, jurisdictions will need to consider the cost impact to drug plans and overall health care system sustainability in making decisions regarding treatment eligibility.

Of Note:

- Severity of liver disease in patients with CHC infection is assessed primarily by fibrosis staging using METAVIR score, and most clinicians consider METAVIR score ≥ F2 to define more severe disease. Extrahepatic manifestations are additional considerations in defining disease severity.
- Patients with more severe disease should be offered treatment first.

Recommendation 2

CDEC recommends ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin as preferred regimens for treatment-naive and peginterferon/ribavirin-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status. The recommended duration of therapy is as per the Health Canada–approved monograph for each regimen.

Conditions:

- Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Reasons for Recommendation 2

- Based on the CADTH systematic review and network meta-analysis (NMA), ledipasvir/sofosbuvir (LDV + SOF) and paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin (PAR/RIT + OMB + DAS ± RBV) demonstrated greater efficacy compared with peginterferon plus ribavirin (PR) and most DAA-PR regimens with respect to SVR for treatment-naive and treatment-experienced patients with CHC genotype 1 infection. There were no statistically significant differences on SVR between LDV + SOF and PAR/RIT + OMB + DAS ± RBV in most analyses.

- In the CADTH cost-effectiveness analysis, both LDV + SOF and PAR/RIT + OMB + DAS ± RBV were cost-effective alternatives compared with PR for patients with genotype 1 infection, regardless of treatment experience or cirrhosis status. The incremental effectiveness, as measured by quality-adjusted life years (QALYs), and incremental cost-utility ratios (ICURs) for these regimens when compared with PR were similar.

Of Note:

- Drug plan costs for LDV + SOF should not exceed the drug plan costs for PAR/RIT + OMB + DAS ± RBV (and vice versa) for any of the subpopulations for which these regimens are approved.
- PAR/RIT + OMB + DAS is approved for use in combination with ribavirin for all patients with CHC genotype 1 infection except those with genotype 1b infection without cirrhosis, for whom the addition of ribavirin is not required. The recommended duration of treatment is 12 weeks for all patients except those with genotype 1a infection and cirrhosis who have had a previous null response to PR, for whom 24 weeks of therapy is recommended.
- The approved treatment duration for LDV + SOF is eight weeks for treatment-naive patients without cirrhosis and baseline HCV ribonucleic acid (RNA) less than 6 million international units per millilitre (IU/mL). In the CADTH systematic review and NMA, LDV + SOF for eight weeks was analyzed in a sensitivity analysis due to the lack of data for the subgroup of patients with baseline HCV RNA < 6 million IU/mL. In treatment-naive patients without cirrhosis (regardless of baseline HCV RNA level), there were no significant differences between this regimen and LDV + SOF for 12 weeks or PAR/RIT + OMB + DAS ± RBV for 12 weeks. LDV + SOF for eight weeks was the most cost-effective option for treatment-naive patients without cirrhosis. The recommended duration of LDV + SOF for treatment-naive patients (including those with cirrhosis) with HCV RNA ≥ 6 million IU/mL and treatment-experienced patients without cirrhosis is 12 weeks, and 24 weeks for treatment-experienced patients with cirrhosis. The eight-week regimen for treatment-naive patients without cirrhosis was approved based on a post-hoc analysis of relapse rates.
- There were no significant differences in SVR rates between daclatasvir/sofosbuvir (DCV + SOF) for 12 weeks and either LDV + SOF or PAR/RIT + OMB + DAS ± RBV for treatment-naive patients without cirrhosis. While DCV + SOF was dominated (i.e., it was less effective and more costly) by LDV + SOF in the cost-effectiveness analysis for this population, the differences in incremental effectiveness as measured by QALYs were small, and unlikely to be consequential in light of the uncertainty inherent in NMAs incorporating evidence from single-arm trials. Therefore, DCV + SOF for 12 weeks may be considered as an alternative for treatment-naive patients without cirrhosis if the drug plan cost does not exceed the costs for LDV + SOF and PAR/RIT + OMB + DAS ± RBV. There was no evidence available for the analysis of DCV + SOF for treatment-naive patients with cirrhosis or for treatment-experienced patients.
- Simeprevir/sofosbuvir (SIM + SOF) for 12 weeks has a Notice of Compliance with conditions (NOC/c) for the treatment of patients with CHC genotype 1 infection, based on data from phase 2 trials for this regimen. In CADTH's systematic review and NMA, the relative risk of achieving SVR was statistically significant in favour of SIM + SOF for 12 weeks versus PR for 48 weeks for treatment-experienced patients with cirrhosis, but not for patients without cirrhosis or for treatment-naive patients. There were no statistically significant differences between SIM + SOF 12 weeks and other all-oral DAA regimens in most comparisons. In terms of cost-effectiveness, SIM + SOF 12 weeks was dominated by LDV + SOF or PAR/RIT + OMB + DAS ± RBV in all subpopulations.
- In the CADTH systematic review and NMA, LDV + SOF, PAR/RIT + OMB + DAS ± RBV, and DCV + SOF were associated with significantly lower risks for rash and anemia than

PR-based treatments, and LDV + SOF and DCV + SOF were also associated with a lower risk for depression compared with PR. The risk of anemia tended to be higher for PAR/RIT + OMB + DAS compared with LDV + SOF, particularly when combined with RBV. The risk of rash was higher with PAR/RIT + OMB + DAS + RBV in treatment-naive patients compared with the same regimen without RBV, LDV + SOF, and DCV + SOF.

- In October 2015, the US Food and Drug Administration (FDA) warned of the risk of serious liver injury with PAR/RIT+ OMB + DAS, mostly in patients with underlying advanced liver disease.[12]
- Data were limited to evaluate HIV-coinfected patients with genotype 1 infection. In the CADTH systematic review and NMA, LDV + SOF, PAR/RIT + OMB + DAS + RBV for 12 weeks, and SOF + RBV for 24 weeks significantly improved SVR compared with PR48 in treatment-naive HIV-coinfected patients with genotype 1 infection. SVR rates were comparable in this population to those observed in patients with CHC genotype 1 monoinfection. One non-comparative study of PAR/RIT + OMB + DAS + RBV for 12 or 24 weeks demonstrated high SVR rates among treatment-experienced HIV-coinfected patients with genotype 1 infection. Cost-effectiveness of treatment for CHC infection for patients with HIV coinfection was not assessed.
- Data to evaluate patients with genotype 1 infection and liver transplant were limited to two studies, one evaluating PAR/RIT + OMB + DAS ± RBV in patients with genotype 1 infection and no or mild fibrosis, and the other evaluating SOF + RBV for 24 weeks in mostly treatment-experienced patients with genotypes 1 (83%), 3 (15%), and 4 (3%) infection. SVR rates were 97% in the study of PAR/RIT + OMB + DAS ± RBV and 70% in the SOF + RBV study. There was no evidence available for patients with genotype 1 infection and decompensated liver disease.

Recommendation 3

CDEC recommends the following as preferred regimens for patients with CHC infection genotypes 2 through 4:

Genotype	PR-Experienced?	Cirrhosis?	Recommended Regimen[a]
2	No	No	SOF + RBV for 12 weeks
		Yes	
	Yes	No	
		Yes	
3	No	No	DCV + SOF for 12 weeks
		Yes	SOF + RBV for 24 weeks
	Yes	No	DCV + SOF for 12 weeks
		Yes	SOF + RBV for 24 weeks
4	No	No	SOF + PR for 12 weeks
		Yes	Insufficient evidence to make a recommendation
	Yes	No	
		Yes	

[a] See "Of Note" subsection for information on other regimens that may also be cost-effective but do not have a Health Canada–approved indication at the present time.

Conditions:

- Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Reasons for Recommendation 3

- Based on the CADTH systematic review and NMA, DAA-based regimens for which evidence was available in patients with CHC infection genotypes 2 through 4 (i.e., SOF + PR, SOF + RBV, DCV + SOF) demonstrated significantly greater efficacy on SVR compared with PR, and there were no significant differences between DAA-based regimens.
- For treatment-naive patients, PR was considered to be the appropriate comparator for DAA-based regimens based on clinical expert opinion. In its deliberations, CDEC gave considerable weight to input from patient groups that PEG-IFN was unacceptable to patients due to its adverse effect profile (except when PEG-IFN–based therapies clearly offered the best prospect of SVR), and to input from clinical experts that PEG-IFN should be avoided whenever possible. For treatment-naive patients with genotype 2 or 3 infection, the most cost-effective PEG-IFN–free regimens approved in Canada were therefore recommended, although CDEC acknowledged that these regimens were unlikely to be considered cost-effective compared with PR for patients without cirrhosis (ICURs of approximately $100,000 per QALY or greater). For treatment-naive patients with genotype 2 or 3 infection and cirrhosis, or genotype 4 infection without cirrhosis, the ICURs for the recommended regimens were more favourable versus PR (between $50,000 and $100,000 per QALY). There was insufficient information available to assess efficacy, safety, or cost-effectiveness of SOF + PR for 12 weeks, the only DAA-based regimen approved for patients with genotype 4 infection, in treatment-naive patients with cirrhosis.
- For PR-experienced patients, subsequent treatment with PR was not considered to be a viable option. For PR-experienced patients with genotype 2 infection, SOF + RBV for 12 weeks was the only approved treatment that could be assessed; it was associated with ICURs of $60,000 per QALY or less compared with no treatment. For genotype 3 infection, DCV + SOF for 12 weeks was the most cost-effective approved DAA-based treatment versus no treatment for patients without cirrhosis, and SOF + RBV for 24 weeks was the only approved treatment that could be assessed for patients with cirrhosis. These regimens were associated with ICURs of approximately $40,000 per QALY or less compared with no treatment. There was insufficient information available to assess efficacy, safety, or cost-effectiveness of SOF + PR for 12 weeks, the only DAA-based regimen approved for patients with genotype 4 infection, in treatment-experienced patients.

Of Note:

- Despite the preference of patients and clinicians to avoid PEG-IFN, CDEC recognized the potential impact on health system sustainability of treating all patients with CHC genotypes 2 through 4 infection with DAA-based regimens.
- In some instances, regimens recommended by the Canadian Association for the Study of the Liver (CASL) guidelines[11] but not currently approved in Canada were the most cost-effective treatments. SOF + PR for 12 weeks is one of the regimens recommended by CASL for genotypes 2 and 3. For genotype 2 infection, SOF + PR for 12 weeks was the most cost-effective regimen for treatment-experienced patients with cirrhosis. For genotype 3 infection, SOF + PR for 12 weeks was the most cost-effective regimen versus PR in treatment-naive patients, and versus no treatment for treatment-experienced patients, regardless of cirrhosis status. The most cost-effective approved treatments for genotype 3 were either associated with very high ICURs compared with SOF + PR for 12 weeks, or were dominated by this regimen. For genotype 4 infection, SOF + RBV for 24 weeks is one of the regimens recommended by the CASL guidelines; it was the most cost-effective regimen for treatment-naive patients with cirrhosis, and for treatment-experienced patients.

- SOF + PR for 12 weeks is indicated for all patients with genotype 4 infection, regardless of treatment experience or cirrhosis status. However, sufficient data for analysis in CADTH's systematic review and NMA were only available for treatment-naive patients without cirrhosis.
- For patients with genotype 3 infection without cirrhosis (regardless of treatment experience), there were no significant differences in SVR rates between SOF + RBV for 24 weeks and the recommended treatment, DCV + SOF for 12 weeks. However, DCV + SOF for 12 weeks was associated with lower total costs and slightly higher QALY gains (ranging from 0.10 to 0.18 QALYs) in the cost-effectiveness analysis compared with SOF + RBV for 24 weeks, resulting in the latter regimen being dominated.
- The CASL guidelines recommend SOF + RBV for 16 weeks as an alternative regimen (to the preferred regimen of SOF + PR for 12 weeks) for patients with genotype 2 infection and cirrhosis. In CADTH's systematic review and NMA, there was no significant difference in SVR rates between 16 weeks and 12 weeks of SOF + RBV in treatment-experienced patients with cirrhosis, while no data for the 16-week regimen were found for treatment-naive patients with cirrhosis.
- Evidence for CHC infection genotypes 2 through 4 was limited to small, uncontrolled trials, and CDEC considered the indirect estimates of effect from the CADTH NMA to be uncertain. The incremental effectiveness, as measured by QALYs and ICURs, for DAA-based regimens compared with PR (or no treatment) was similar, and unlikely to be consequential in light of the uncertainty inherent in NMAs incorporating evidence from single-arm trials.
- DCV + SOF for 24 weeks is approved in Canada for the treatment of patients with genotype 2 infection, and patients with genotype 3 infection with cirrhosis. DCV + SOF for 12 weeks is approved for patients with genotype 3 infection without cirrhosis. There was no evidence for the approved duration of DCV + SOF in genotype 2 infection that could be incorporated into the CADTH systematic review and NMA. There was also no evidence for DCV + SOF for 24 weeks that could be analyzed in the NMA or cost-effectiveness analysis of patients with genotype 3 infection and cirrhosis.
- PAR/RIT+ OMB + RBV for 12 weeks for the treatment of genotype 4 infection was submitted to the CADTH Common Drug Review (CDR) as a pre-NOC submission during the course of CADTH's Therapeutic Review, and this regimen received NOC in October 2015. Sensitivity analyses were carried out to incorporate the only trial (PEARL-I) that has studied this regimen into the NMA. Evidence was available only for patients without cirrhosis. PAR/RIT+ OMB + RBV for 12 weeks was not significantly different with respect to SVR rate compared with SOF+ RBV for 24 weeks, or SOF + PR for 12 weeks. In October 2015, the FDA warned of the risk of serious liver injury with PAR/RIT+ OMB + RBV, mostly in patients with underlying advanced liver disease.[12]
- In the CADTH systematic review and NMA, there were no significant differences in the risk of rash or depression between DCV + SOF for 12 weeks, SOF + PR for 12 weeks, SOF + RBV for 12 weeks, and SOF + RBV for 24 weeks in treatment-naive patients. DCV + SOF for 12 weeks was associated with significantly less anemia in this population than SOF + RBV for 24 weeks and SOF + PR for 12 weeks, and SOF + PR for 12 weeks was associated with more anemia than SOF + RBV for 12 weeks. In treatment-experienced patients, there were no significant differences between SOF + PR for 12 weeks, SOF + RBV for 12 weeks or SOF + RBV for 24 weeks in the risk of rash or anemia, or between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks in the risk of depression. There was no evidence to include DCV + SOF in the analyses of these adverse events for treatment-experienced patients.
- Data were limited to evaluate HIV-coinfected patients with CHC infection genotypes 2 through 4, although the following regimens demonstrated high SVR rates in individual studies: SOF + RBV for 12 weeks in genotype 2; SOF + RBV for 24 weeks in genotype 3;

SOF + RBV for 24 weeks and SOF + PR for 12 weeks in genotype 4. There were no data for treatment-experienced patients with HIV coinfection. Cost-effectiveness of treatment for CHC infection for patients with HIV coinfection was not assessed.
- Data to evaluate patients with genotypes 2, 3, or 4 infection and liver transplant were limited to one study evaluating SOF + RBV for 24 weeks in mostly treatment-experienced patients with genotypes 1 (83%), 3 (15%), and 4 (3%) infection. None of the patients with genotype 4 infection achieved SVR, and results were not reported separately for patients with genotype 3 infection. There was no evidence available for patients with genotype 2, 3, or 4 infection and decompensated liver disease.

Recommendation 4

CDEC considered there to be insufficient evidence to make a recommendation for patients with CHC genotype 5 or 6 infection.

Reasons for Recommendation 4

- A trial of SOF + PR for 12 weeks in treatment-naive patients with CHC genotypes 1, 4, 5, or 6 infection enrolled one patient with genotype 5 infection, and six patients with genotype 6 infection. All patients achieved SVR in this study. A second trial, of SOF + PR for 24 weeks in treatment-naive patients with CHC genotypes 1, 4, 5, or 6 infection, enrolled five patients with genotype 6 infection, all of whom achieved SVR.

Of Note:

- None of the DAA regimens available in Canada are approved for use in CHC genotype 5 or 6 infection.
- The CASL guidelines recommend SOF + PR for 12 weeks for the treatment of CHC genotype 5 infection, and LDV + SOF for 12 weeks (preferred) or SOF + PR for 12 weeks (alternative) for the treatment of CHC genotype 6 infection.[11]

Recommendation 5

CDEC recommends LDV + SOF as the preferred regimen for patients with genotype 1 infection previously treated with a protease inhibitor-PR regimen, regardless of cirrhosis status. CDEC considered there to be insufficient evidence to make a recommendation for patients previously treated with an all-oral DAA regimen.

CDEC considered there to be insufficient evidence to make a recommendation for patients with non-genotype 1 CHC infection previously treated with a DAA-based regimen.

Conditions:

- Treatment should be initiated by physicians with experience in the management of patients with CHC infection.

Reasons for Recommendation 5

- Data for the efficacy and safety of treatments for CHC infection in patients previously treated unsuccessfully with DAA-PR regimens were limited to four studies that reported SVR rates specifically in this population. The largest of these was ION-2, in which SVR rates among patients with genotype 1 infection and prior treatment failure on DAA-PR were as follows:

94% with LDV + SOF for 12 weeks (n = 66); 97% with LDV + SOF + RBV for 12 weeks (n = 64); 98% with LDV + SOF for 24 weeks (n = 50); and 100% with LDV + SOF + RBV for 24 weeks (n = 51).
- Only one study reported SVR rates for patients previously treated with an all-oral DAA regimen. In this study, all 14 patients with CHC genotype 1 infection previously treated with SOF + RBV achieved SVR with LDV + SOF for 12 weeks.

Of Note:
- Limited evidence was also available for the use of SOF + PR for 12 weeks from a study of 80 patients with CHC genotype 1 infection without cirrhosis and prior experience with DAA-PR, in which the reported SVR rate was 79%.
- Due to the higher SVR rates achieved with DAA-based regimens, the number of patients experiencing treatment failure on these regimens is small. Based on input from clinical experts, patients with genotype 3 infection and cirrhosis may be more likely to experience treatment failure on initial therapy than other patients with CHC infection.
- Resistance testing may be used to guide the choice of a future regimen in patients experiencing treatment failure on initial therapy; however, such testing is not available in all centres. Furthermore, there are insufficient data on which to make these recommendations at present.
- Due to the lack of evidence, and depending upon disease severity, consideration may be given to withholding further therapy for patients experiencing treatment failure on initial therapy.

Discussion Points

- The relatively small size and uncontrolled nature of the available studies for DAA-based regimens did not allow for a thorough assessment of harms. Emerging information about both efficacy and harms associated with these regimens should be integrated into listing decisions.
- Approximately 25% of patients acutely infected with HCV spontaneously clear the infection. The diagnosis of CHC infection requires confirmation of serum HCV RNA at six months after initial testing. Once chronic infection has been confirmed, repeat HCV RNA testing is not required because spontaneous clearance of chronic infection is extremely rare. While CHC infection is usually asymptomatic until liver fibrosis is advanced, some patients may experience symptoms such as fatigue or “brain fog” in earlier stages of the disease, while others may experience no symptoms even with cirrhosis.
- CDEC discussed the limitations of fibrosis staging methods such as FibroScan with respect to accuracy and test–retest reliability. In particular, it was noted that there is often concern that patients assessed as having a METAVIR score of F3 may have undetected cirrhosis, and that treatment decisions may be made accordingly.
- CDEC noted that the evidence for genotypes 2 through 4 was particularly limited with respect to both the number and size of trials in light of the considerable prevalence of these infections in Canada.
- CDEC discussed the smallest difference in SVR rates between regimens that would be clinically meaningful. No evidence was found in the literature; however, based on expert input, a difference of less than 5% was considered unlikely to reflect a clinically important difference.
- Given the lack of trials directly comparing newer regimens for CHC infection, CDEC discussed the potential value of real-world evidence generation in this area for assessing

comparative efficacy and safety, including long-term measures such as liver-related morbidity and mortality.
- CDEC noted the observation from clinical experts that there may be considerable variability in measured HCV RNA levels, including test–retest variability. This may have implications for treatment decisions involving LDV + SOF for eight weeks, which is indicated for treatment-naive, non-cirrhotic patients with genotype 1 infection and baseline HCV RNA < 6 million IU/mL.
- CDEC noted that of the Health Canada–approved regimens for CHC infection, only SIM + SOF for the treatment of patients with CHC genotype 1 infection has not yet been submitted to CDR.

Research Gaps

CDEC noted the following research gaps related to treatments for CHC infection:
- Lack of head-to-head trials comparing DAA-based regimens with one another
- Paucity of evidence for genotypes 5 and 6
- Lack of adequate studies to guide therapy for patients experiencing treatment failure with a DAA-based regimen
- Efficacy and safety of DAA-based regimens for patients with CHC infection and chronic kidney disease, or decompensated liver disease.

Patient Group Input

Committee discussions were informed by submissions to CADTH by two patient groups: the Canadian Treatment Action Council, and the HepCBC Hepatitis C Education and Prevention Society. The following points summarize the concerns of patients and caregivers as documented in the patient group submissions.
- Caregivers find it difficult to support their loved one during treatment and often experience poverty, isolation, and uncertainty about the future. Poverty ensues as medical expenditures increase, as the patient is unable to contribute to family responsibilities, and as caregiving requirements disrupt the caregiver's own work.
- The social stigma associated with HCV infection is of concern for patients and their caregivers. Driven by the emergence of promising treatments, patients in the baby-boom cohort have become more willing to be open about their infection; however, patients coinfected with HIV experience increased stigma and treatment challenges.
- While it is recognized that interferon and/or ribavirin may be necessary in some cases, there is an overwhelming consensus from patients that interferon in particular but also ribavirin should be consigned to history as soon as possible due to their debilitating side effects and low efficacy. Administering interferon can also be a source of anxiety for patients with a history of injection drug use.
- Patients indicated a need for interferon-free treatments with increased SVR rates, shorter treatment durations, fewer side effects, and effectiveness across all genotypes, stages of liver disease, and previous treatment responder types. One patient group indicated that a large percentage of patients they come into contact with were being "warehoused," either by doctors or by themselves, rejecting the idea of taking therapies containing interferon and/or ribavirin, knowing that vastly superior drugs are already approved, although not yet accessible, or are very close to being approved.
- Patients are concerned that the prices of these drugs will be so high that CADTH (and/or provincial Pharmacare plans) will either not approve the treatment at all or implement

coverage criteria that require patients to undergo and fail very challenging standard treatments (with both interferon and ribavirin) before having access to newer DAAs. Delaying treatment until liver disease is more advanced affects patients' physical and mental well-being.
- Patients noted that it is frustrating for many patients to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment and suggest that patients' mental health, any extrahepatic manifestations they may have, and the state of their immune system be considered in treatment decisions. The sooner a person is effectively treated (i.e., cured), the sooner a patient's quality of life improves, and the less chance he or she has of inadvertently infecting someone else.

Summary of the Evidence

Clinical Evidence

The Committee considered the results of CADTH's systematic review and NMA of published literature on interventions of interest for the treatment of CHC infection. The review was an update to the 2014 CADTH Therapeutic Review on DAAs for CHC genotype 1 infection, and also extended the scope to genotypes 2 through 6. Regimens were included if approved for use in Canada or recommended in major Canadian or US guidelines even if not approved. A number of emerging regimens were also included in the analysis. As most newer regimens have been approved on the basis of uncontrolled or historically controlled studies, such trial designs were included in the review.

The review included 63 new publications describing 67 unique studies, in addition to 10 studies from the previous Therapeutic Review:

- In genotype 1, there were 35 studies for treatment-naive patients (additional five studies for emerging treatments), and 26 studies for treatment-experienced patients (additional two studies for emerging treatments).
- In genotype 2, there were five studies for treatment-naive patients, and five studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 2).
- In genotype 3, there were three studies for treatment-naive patients, and six studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 3).
- In genotype 4, there were three studies for treatment-naive patients, and two studies for treatment-experienced patients (no studies for emerging treatments were identified for genotype 4).
- In genotype 5, there was one study for treatment-naive patients, and no studies were identified for treatment-experienced patients.
- For genotype 6, there were two studies for treatment-naive patients (additional one study for emerging treatments), and no studies were identified for treatment-experienced patients.
- Patients with HIV coinfection were included in four studies of treatment-naive patients (three studies were on genotype 1 patients and one study on genotypes 1 to 6 patients) and four with combined treatment-naive and -experienced patients (two studies on genotype 1 patients, one study on genotypes 1 to 3 patients, and one study on genotypes 1 to 4 patients). Two studies identified were in the post-liver transplant setting. No studies of patients with hepatitis B virus or tuberculosis coinfection met the inclusion criteria for the systematic review, as these coinfections were generally specified as exclusion criteria in many of the included studies.

The main efficacy outcome of interest was SVR at 12 weeks (SVR12) or 24 weeks. Key safety outcomes were rash, depression, and anemia.

Bayesian NMAs were conducted for SVR12 and key safety outcomes (i.e., rash, anemia, and depression) for both treatment-naive and treatment-experienced patients. Single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm. SVR was also analyzed according to cirrhosis status within treatment-naive and -experienced patients, and a number of subgroup analyses were performed. Treatment-experienced patients were further analyzed based on their response to prior treatment; i.e., whether they experienced relapse, partial response, or null response. The review also assessed the available evidence for patients previously treated with DAA-based regimens.

Of the 77 studies included in the systematic review, 31 studies were randomized controlled trials (RCTs). In general, the included RCTs were of adequate quality. The weakest domain was blinding for subjective outcomes, on which more than half of the included RCTs were assessed as being at high or unclear risk of bias. The remaining studies evaluated interventions of interest in single groups, or cohorts, of study participants with either no control group, or employed comparisons to historical control populations. For these studies, the rate of attrition was the only criterion that could be consistently identified and evaluated across studies. Patient attrition can bias outcomes if patients with missing outcome data are excluded from the analysis and have less favourable results than patients without missing data. In studies of treatment-naive patients, attrition rates ranged from 0% to 17%. In studies of treatment-experienced patients reporting the necessary information, attrition rates ranged from 0% to 2.5%. In the 13 studies with both treatment-naive and -experienced patients, attrition rates ranged from 0% to 48%.

With respect to baseline characteristics in the included trials, enrolled patients were adults aged 18 and older and the proportion of male participants was generally much higher than 50% (range 28% to 100%). Patients enrolled in the studies of treatment-naive patients were mostly without cirrhosis (range 78% to 100%, when reported). In the studies of treatment-experienced patients, patients with cirrhosis were included in proportions ranging from 0% to 100%. Baseline viral load, when reported, ranged from 5.6 to 6.8 IU/mL on average. Previous treatment experience in the included study populations was predominantly with PR; few studies reported treatment experience with DAA plus PR or with all-oral DAA regimens.

Genotype 1, Treatment-Naive

The evidence network for SVR12 in treatment-naive genotype 1 patients included 35 studies and a total of 6,766 participants. All of the DAA treatment strategies under review, except SIM + SOF for 12 weeks, significantly improved SVR compared with PR for 48 weeks (relative risk [RR] range 1.48 to 1.86). LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS ± RBV for 12 weeks significantly improved SVR compared with SOF + RBV for 24 weeks, response-guided therapy (RGT) with SIM-PR, and SOF + PR for 12 weeks (result was statistically non-significant for PAR/RIT + OMB + DAS for 12 weeks versus SOF + PR for 12 weeks). There were no statistically significant differences between LDV + SOF for 12 weeks, DCV + SOF for 12 weeks, and PAR/RIT + OMB + DAS ± RBV for 12 weeks.

Results of the subgroup analysis were consistent with those for the overall treatment-naive population, especially for the comparisons between interferon-free regimens; there were no significant differences in SVR12 among LDV + SOF for 12 weeks, DCV + SOF for 12 weeks, and PAR/RIT + OMB + DAS ± RBV for 12 weeks where these regimens could be compared with one another. Due to the lack of stratified baseline data by prior treatment experience for

PAR/RIT + OMB + DAS ± RBV for 12 weeks, this regimen was included only for patients with cirrhosis, and patients with HIV coinfection, as part of sensitivity analyses based on certain assumptions. There were no data for DCV + SOF specific to patients with genotype 1a or genotype 1b infection, and no trials for this regimen in patients with cirrhosis or HIV coinfection.

Table 1 summarizes selected subgroup results for SVR in treatment-naive patients with genotype 1 infection.

Table 1: Summary of Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Naive Patients With Genotype 1 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Genotype 1a	17 studies; 3,594 participants	No significant differences between LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS + RBV for 12 weeks.
Genotype 1b	20 studies; 2,379 participants	No significant differences between LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS for 12 weeks.
Patients with cirrhosis	14 studies; 539 participants	No significant differences between PAR/RIT + OMB + DAS + RBV for 12 weeks, LDV + SOF for 12 weeks ± RBV12, and SOF + PR for 12 weeks.
Patients without cirrhosis	29 studies; 6,018 participants	No significant differences between SOF8 + LDV8, LDV + SOF for 12 weeks, DCV + SOF for 12 weeks, and PAR/RIT + OMB + DAS ± RBV for 12 weeks.
HIV coinfection	6 studies; 410 participants	No significant difference between LDV + SOF for 12 weeks and SOF + RBV for 24 weeks. Also no significant differences between these regimens and PAR/RIT + OMB + DAS + RBV for 12 weeks.

DAS = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LDV8 = ledipasvir for 8 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RBV12 = ribavirin for 12 weeks; RIT = ritonavir; SOF = sofosbuvir; SOF8 = sofosbuvir for 8 weeks.

LDV + SOF for eight weeks is indicated for treatment-naive patients with genotype 1 infection without cirrhosis that have a baseline HCV RNA level of less than 6 million IU/mL. Due to the specialized indication, this regimen was considered only in a sensitivity analysis. Compared with PR for 48 weeks, LDV + SOF for eight weeks significantly increased SVR, and there were no significant differences compared with LDV + SOF for 12 weeks, PAR/RIT + OMB + DAS ± RBV for 12 weeks, or DCV + SOF for 12 weeks. There was a marginally significant improvement in SVR when LDV + SOF for eight weeks was compared with SOF + PR for 12 weeks.

Genotype 1, Treatment-Experienced

This analysis included 22 studies and a total of 4,146 participants. Compared with PR for 48 weeks, all of the DAA treatment strategies significantly improved SVR (RR ranged from 2.72 to 3.75). No significant differences were found when LDV + SOF for 12 weeks was compared with PAR/RIT + OMB + DAS ± RBV for 12 weeks. There were no trials for DCV + SOF in treatment-experienced patients.

Results of the subgroup analyses were generally consistent with those for the overall treatment-experienced population in that no significant differences in SVR were found in all but two subgroups when LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS ± RBV for 12 weeks were compared against each other. One exception was the subgroup analysis of patients

without cirrhosis, in which PAR/RIT + OMB + DAS + RBV for 12 weeks significantly improved SVR compared with LDV + SOF for 12 weeks, and the second was the subgroup analysis of patients with genotype 1b infection, in which PAR/RIT + OMB + DAS for 12 weeks significantly improved SVR compared with LDV + SOF for 12 weeks. Due to the lack of stratified baseline data by prior treatment experience for PAR/RIT + OMB + DAS ± RBV for 12 weeks, this regimen was included only in the analysis of patients with cirrhosis as part of a sensitivity analysis based on certain assumptions. LDV + SOF for 12 weeks could not be included in any of the subgroup analyses by type of prior response — i.e., prior relapse, prior partial response, and prior null response — due to lack of data. As well, analysis by type of prior response was not possible for interferon-free regimens in patients with cirrhosis, due to lack of data. Table 2 presents selected results for the subgroup analysis of SVR for treatment-experienced patients with genotype 1 infection.

Table 2: Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Experienced Patients With Genotype 1 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Genotype 1a	10 studies; 1,683 participants	No significant differences between LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS + RBV for 12 weeks.
Genotype 1b	15 studies; 2,053 participants	PAR/RIT + OMB + DAS for 12 weeks significantly improved SVR compared with LDV + SOF for 12 weeks.
Patients with cirrhosis	15 studies; 850 participants	No significant differences between PAR/RIT + OMB + DAS + RBV for 12 weeks, LDV + SOF ± RBV for 12 weeks, SOF + LDV for 24 weeks, SIM + SOF for 12 weeks, or SOF + PR for 12 weeks.
Patients without cirrhosis	16 studies; 3,038 participants	PAR/RIT + OMB + DAS + RBV for 12 weeks significantly improved SVR compared with LDV + SOF for 12 weeks.
HIV coinfection	1 study; 21 participants	PAR/RIT + OMB + DAS + RBV for 12 or 24 weeks demonstrated high SVR rates.
Treatment-experienced with prior relapse	7 studies; 741 participants	No significant difference between PAR/RIT + OMB + DAS ± RBV for 12 weeks and LDV + SOF for 12 weeks.
Treatment-experienced with prior partial response	10 studies; 840 participants.	PAR/RIT + OMB + DAS + RBV for 12 weeks significantly improved SVR compared with SIM12 + PR for 48 weeks. No significant difference between PAR/RIT + OMB + DAS for 12 weeks, PAR/RIT + OMB + DAS + RBV for 12 weeks or SIM/PR 12/48 weeks.
Treatment-experienced with prior null response	13 studies; 1,403 participants.	PAR/RIT + OMB + DAS + RBV for 12 weeks significantly improved SVR compared with SOF + PR for 12 weeks and SIM/PR 12/48 weeks. No significant difference between PAR/RIT + OMB + DAS for 12 weeks and PAR/RIT + OMB + DAS + RBV for 12 weeks or SIM/PR 12/48 weeks.

DAS = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LDV8 = ledipasvir for 8 weeks; LDV24 = ledipasvir for 24 weeks; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; PR12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; RBV12 = ribavirin for 12 weeks; RIT = ritonavir; SIM = simeprevir; SIM12 = simeprevir for 12 weeks; SOF = sofosbuvir; SOF8 = sofosbuvir for 8 weeks; SOF12 = sofosbuvir for 12 weeks; SOF24 = sofosbuvir for 24 weeks; SVR = sustained virologic response.

Genotype 2, Treatment-Naive

This analysis included five studies and a total of 116 participants. Overall, three different treatment regimens were considered (PR for 24 weeks, SOF + RBV for 12 weeks, and SOF + PR for 12 weeks). Compared with PR for 24 weeks, SOF + RBV for 12 weeks significantly improved SVR, whereas SOF + PR for 12 weeks was not significantly different from PR for 24 weeks (RRs ranged from 1.13 to 1.20). When SOF + RBV for 12 weeks and SOF + PR for 12 weeks were compared, no significant difference was identified. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in genotype 2 infection treatment-naive patients that could be incorporated into the CADTH systematic review and NMA.

Results of the subgroup analyses were consistent with those for the overall treatment-naive population; however, SOF + PR for 12 weeks could not be included in the subgroup analysis of patients with cirrhosis due to limitations of the data. Table 3 presents selected results for the subgroup analysis of SVR for treatment-naive patients with genotype 2 infection.

Table 3: Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Naive Patients With Genotype 2 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	5 studies; 37 participants.	Compared with PR for 24 weeks, SOF + RBV for 12 weeks significantly improved SVR in genotype 2 treatment-naive patients
Patients without cirrhosis	6 studies; 278 participants.	Compared with PR for 24 weeks, only SOF + RBV for 12 weeks significantly improved SVR No significant difference in SVR between SOF + RBV for 12 weeks and SOF + PR for 12 weeks
HIV coinfection	Two studies reported on the use of SOF + RBV for 12 weeks (SVR rate 88% to 89% in 45 patients). Data were insufficient for subgroup analyses.	

PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

Genotype 2, Treatment-Experienced

This analysis included four studies and a total of 172 participants. Based on clinical expert opinion, PR therapy was not considered to be appropriate as a comparator in this population. Overall, three different treatment regimens were considered (SOF + RBV for 12 weeks, SOF + RBV for 16 weeks, and SOF + PR for 12 weeks). Neither SOF + RBV for 16 weeks nor SOF + PR for 12 weeks significantly improved SVR compared with SOF + RBV for 12 weeks (RRs ranged from 0.86 to 1.07), but SOF + PR for 12 weeks significantly improved SVR when compared with SOF + RBV for 16 weeks. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in treatment-experienced patients with genotype 2 infection that could be incorporated into the CADTH systematic review and NMA.

Results of subgroup analyses were generally consistent with those for the overall treatment-experienced population, although SOF16 + RBV16 could not be included in the analysis of patients without cirrhosis. As well, there were no data to allow for analysis of treatment-experienced patients with genotype 2 infection and HIV coinfection.
Table 4 presents selected results from subgroup analyses of SVR for treatment-experienced patients with genotype 2 infection.

Table 4: Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Experienced Patients With Genotype 2 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	4 studies; 172 participants	No statistically significant differences in SVR between SOF + RBV for 12 weeks, SOF16 + RBV16 and SOF12 + PR12
Patients without cirrhosis	3 studies; 95 participants	SOF + PR for 12 weeks did not significantly improve SVR when compared with SOF + RBV for 12 weeks.

PR = pegylated interferon plus ribavirin; PR12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; RBV16 = ribavirin for 16 weeks; SOF = sofosbuvir; SOF12 = sofosbuvir for 12 weeks; SOF16 = sofosbuvir for 16 weeks; SVR = sustained virologic response.

Genotype 3, Treatment-Naive

This analysis included three studies and a total of 237 participants. Compared with PR for 48 weeks, SOF + RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.31 to 1.37), and there were no significant differences between these regimens. It should be noted that SOF + PR for 12 weeks could be brought into the NMA only as part of a sensitivity analysis informed by clinical expert input in which the results of a major trial (BOSON), published in abstract form at the time of the analysis, were incorporated.

Results of subgroup analyses were consistent with those for the overall treatment-naive population, although DCV + SOF for 12 weeks could not be included in the subgroup analysis of patients with cirrhosis due to lack of data. Table 5 presents selected results for the subgroup analyses of SVR for treatment-naive patients with genotype 3 infection. Data were insufficient to perform NMA for patients with genotype 3 infection coinfected with HIV, as only a single study was identified; it reported an SVR rate of 91% in 51 patients treated with SOF24 + RBV24.

Table 5: Subgroup Analysis Results for Sustained Virologic Response for Treatment - Naive Patients With Genotype 3 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	2 studies; 16 participants	Compared with PR for 48 weeks, SOF + RBV for 24 weeks significantly improved SVR. No significant difference between SOF12 + PR12 and SOF + RBV for 24 weeks.
Patients without cirrhosis	3 studies; 221 participants	Compared with PR for 48 weeks, SOF + RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR. No significant differences between these 3 regimens.

DCV = daclatasvir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

Genotype 3, Treatment-Experienced

This analysis included five studies and a total of 269 participants. Compared with PR for 48 weeks, SOF + RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.52 to 1.72). No statistically significant differences were observed between these three regimens.

Results of subgroup analyses were consistent with those for the overall treatment-experienced population; however, there were no statistically significant differences in SVR rates in the subgroup of patients without cirrhosis between SOF + PR for 12 weeks and PR for 48 weeks. There was no evidence for DCV + SOF 24 weeks (the approved duration) that could be analyzed in the NMA of patients with genotype 3 infection and cirrhosis. Table 6 presents results for the subgroup analysis of SVR for treatment-experienced patients with genotype 3 infection. The only studies in treatment-experienced patients with genotype 3 infection and HIV coinfection were two trials of SOF + RBV for 24 weeks (SVR rates were 86% in one study of 49 patients and 94% in the second study of 17 patients).

Table 6: Subgroup Analysis Results for Sustained Virologic Response for Treatment-Experienced Patients With Genotype 3 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	4 studies; 88 participants	Compared with PR for 48 weeks, SOF + RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR. No significant difference between SOF + RBV for 24 weeks and SOF + PR for 12 weeks.
Patients without cirrhosis	5 studies; 181 participants	Compared with PR for 48 weeks, SOF + RBV for 24 weeks, DCV + SOF for 12 weeks and SOF12 + PR12 significantly improved SVR. No significant differences between SOF24 + RBV 24, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks.

DCV = daclatasvir; PR = pegylated interferon plus ribavirin; PR12 = pegylated interferon plus ribavirin for 12 weeks; RBV = ribavirin; SOF = sofosbuvir; SOF12 = sofosbuvir for 12 weeks; SVR = sustained virologic response.

Genotype 4, Treatment-Naive

This analysis included three studies involving a total of 87 participants. Compared with PR for 48 weeks, SOF + RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR, whereas SOF + RBV for 12 weeks was not significantly different from PR for 48 weeks. SOF + PR for 12 weeks was significantly better than SOF + RBV for 12 weeks for improving SVR.

Results of the subgroup analyses were consistent with those for the overall treatment-naive population. In non-cirrhotic patients, SOF + RBV for 24 weeks did not significantly improve SVR when compared with PR.
Table 7 presents selected results for the subgroup analysis of SVR for treatment-naive patients with genotype 4 infection. Only two studies reported results for treatment-naive patients with genotype 4 infection and HIV coinfection: one study of SOF + RBV for 24 weeks reporting a SVR rate of 84% in 31 patients; and one study of SOF + PR for 12 weeks reporting a SVR rate of 91% in 23 patients with genotypes 1 through 4.

SOF + PR for 12 weeks is currently the only regimen indicated for patients with genotype 4 infection. Due to lack of stratified data, SOF + PR for 12 weeks could not be included in the base-case subgroup analysis of patients by cirrhosis status. A sensitivity analysis was undertaken after the draft Clinical Review report[8] was posted for stakeholder feedback, in which SOF + PR for 12 weeks was included in the subgroup analysis of non-cirrhotic patients based on certain assumptions. It was found that SOF + PR for 12 weeks significantly improved SVR in comparison to PR (RR [95% credible interval] 1.48 [1.27 to 1.55]) and that SOF + PR for 12 weeks was not significantly different from SOF + RBV for 12 weeks or SOF + RBV for 24 weeks. The assumptions allowing for the analysis of SOF + PR for 12 weeks in non-cirrhotic patients could not be applied to the subgroup analysis of patients with cirrhosis.

Table 7: Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Naive Patients With Genotype 4 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	2 studies; 14 participants	Compared with PR for 48 weeks, SOF + RBV for 24 weeks significantly improved SVR. SOF + RBV for 12 weeks was not significantly different from PR for 48 weeks for improving SVR.
Patients without cirrhosis	2 studies	There were no statistically significant differences between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks when compared with PR for 48 weeks or to one another.

PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

PAR/RIT+ OMB + RBV for 12 weeks was submitted to CDR as a pre-NOC submission during the course of CADTH's Therapeutic Review, and received a NOC for the treatment of genotype 4 infection in October 2015. Sensitivity analyses were carried out to incorporate the only trial (PEARL-I) that has studied this regimen into the NMA. Evidence was available only for patients without cirrhosis. In treatment-naive patients without cirrhosis, PAR/RIT+ OMB + RBV for 12 weeks was significantly better in terms of SVR compared with PR48, and there were no significant differences between this regimen and SOF + RBV for 24 weeks, or SOF + PR for 12 weeks.

Genotype 4, Treatment-Experienced

This analysis included two studies and a total of 76 participants. There was no statistically significant difference between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks.

Results of the subgroup analyses were consistent with those for the overall treatment-experienced population. Table 8 presents results for the subgroup analysis of SVR for treatment-experienced patients with genotype 4 infection. No studies reported on genotype 4 treatment-experienced patients with HIV coinfection.

Table 8: Selected Subgroup Analysis Results for Sustained Virologic Response for Treatment-Experienced Patients With Genotype 4 Infection

Subgroup	Evidence Included in the Analysis	Main Findings
Patients with cirrhosis	2 studies; 28 participants	There was no statistically significant difference between SOF12 + RBV12 and SOF + RBV for 24 weeks
Patients without cirrhosis	2 studies; 48 participants	There was no statistically significant difference between SOF + RBV for 12 weeks and SOF + RBV for 24 weeks

PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

In sensitivity analyses incorporating data from the PEARL-I study for PAR/RIT + OMB + RBV for 12 weeks into the NMA for treatment-experienced patients without cirrhosis, there were no significant differences between PAR/RIT + OMB + RBV for 12 weeks and SOF + RBV for 24 weeks. No evidence was available for this regimen in treatment-experienced patients with cirrhosis.

Genotypes 5 and 6

Only two studies (NEUTRINO and ATOMIC) evaluated a regimen for genotypes 5 and 6 infection that is currently on the market in Canada. All six patients with genotype 6 infection and the single patient with genotype 5 infection who received SOF + PR for 12 weeks in the NEUTRINO study achieved SVR12. All five patients with genotype 6 who received SOF24 + PR24 in the ATOMIC study achieved SVR12; no patients with genotype 5 were included in ATOMIC study. It should be noted that none of the DAA-based regimens currently available in Canada are approved for the treatment of genotypes 5 and 6 infection.

Direct-Acting Antiviral–Experienced

Nine studies included patients who had previously been treated with a DAA-containing regimen. Eight of these reported treatment experience with either PR alone or a DAA + PR or RBV. Combined results were often presented, such that it was not usually possible to discern efficacy specifically among DAA-experienced patients. Sample sizes for the studies ranged between 14 and 441. LDV + SOF (12-week and 24-week ± RBV) was the most frequently studied treatment regimen (seven studies). With the exception of one small study (n = 14) that included patients with HCV infection genotypes 1 through 4, all studies reported results from adults with genotype 1 infection.

The ION-2 study reported that in patients with cirrhosis who had previously received a protease inhibitor + PR, SVR12 was achieved in 85.7% (12 of 14), 84.6% (11 of 13), 100% (14 of 14), and 100% (13 of 13) of patients receiving LDV + SOF for 12 weeks, LDV + SOF + RBV for 12 weeks, LDV + SOF for 24 weeks, and LDV + SOF + RBV for 24 weeks, respectively. In non-cirrhotic patients, SVR12 was achieved in 96.2% (50 of 52), 100% (51 of 51), 97.2% (35 of 36), and 100% (38 of 38) of patients receiving LDV + SOF for 12 weeks, LDV + SOF + RBV for 12 weeks, LDV + SOF for 24 weeks, and LDV + SOF + RBV for 24 weeks, respectively.

Evidence was also available for the use of SOF12 + PR 12 from a study of 80 patients with CHC genotype 1 infection without cirrhosis and prior experience with DAA-PR, in which the reported SVR rate was 79%. Finally, one study reported data for the use of LDV + SOF for 12 weeks for patients with genotype 1 infection who had relapsed after receiving a DAA-only regimen (SOF + RBV); 14 of 14 patients achieved SVR12 in this study.

Liver Transplant Recipients — All Genotypes

Two studies reported SVR rates for liver transplant recipients with CHC infection. One study reported SVR in a group of 40 patients infected with mixed genotypes (1 [83%], 2 [0%], 3 [15%], 4 [3%]) and mixed treatment experience (88% experienced). Patients were treated with SOF + RBV for 24 weeks, and 70% achieved SVR at 12 weeks. Results were additionally presented by genotype and METAVIR score for those who achieved SVR. Fifty-seven per cent of patients with genotype 1a, 21% of patients with genotype 1b or 3, and 0% of patients with genotype 4 achieved SVR12. Of the patients with a METAVIR score of F4 (considered cirrhotic), 36% achieved SVR12. Outcomes were not presented according to previous treatment status.

A second study reported SVR in adult liver transplant recipients with genotype 1 (85% genotype 1a) and mild or no fibrosis. Thirty-four participants received a once-daily dose of PAR/RIT + OMB + DAS ± RBV for 24 weeks (RBV dose was at the discretion of the investigator). Of the 34 study participants, 33 (97%) achieved SVR.

A phase 2, open-label study (SOLAR-1) that assessed LDV + SOF + RBV for 12 weeks and LDV + SOF + RBV for 24 weeks in patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation, and patients who had undergone liver transplantation, was published shortly after the literature cut-off date of the CADTH systematic review.[13] Response rates in the 12- and 24-week treatment groups were similar. SVR12 was achieved by 86% to 89% of patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. In transplant recipients, SVR was achieved by 96% to 98% of patients without cirrhosis or with compensated cirrhosis; 85% to 88% of patients with moderate hepatic impairment; 60% to 75% of patients with severe hepatic impairment; and by all six patients with fibrosing cholestatic hepatitis.

Safety

Safety outcomes were assessed across genotypes, but separately for treatment-naive and treatment-experienced patients. Among treatment-naive patients, LDV + SOF for 12 weeks, PAR/RIT + OMB + DAS ± RBV for 12 weeks, and DCV + SOF for 12 weeks were associated with significantly lower risks for anemia than PR-based treatments, but only LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS for 12 weeks were significantly associated with less rash and depression compared with PR-based treatments. For rash, PAR/RIT + OMB + DAS + RBV for 12 weeks was less favourable than LDV + SOF for 12 weeks, and PAR/RIT + OMB + DAS for 12 weeks. There was no significant difference between DCV + SOF for 12 weeks and any of the interferon-free regimens. For anemia, PAR/RIT + OMB + DAS ± RBV for 12 weeks was less favourable than LDV + SOF for 12 weeks. There was no significant difference between DCV + SOF for 12 weeks and PAR/RIT + OMB + DAS ± RBV for 12 weeks or LDV + SOF for 12 weeks on this outcome. For depression, PAR/RIT + OMB + DAS + RBV for 12 weeks and DCV + SOF for 12 weeks were less favourable than LDV + SOF for 12 weeks. The result for PAR/RIT + OMB + DAS + RBV should be considered in context of the patient population enrolled in the only study contributing data for this outcome, which consisted of injection drug users on stable methadone treatment that was likely at higher risk for comorbid depression compared with the broader population of patients with CHC infection.

For treatment-experienced patients, LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV + SOF for 12 weeks and PAR/RIT + OMB + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments. For rash there was no significant difference between PAR/RIT + OMB + DAS ± RBV for 12 weeks and LDV + SOF for 12 weeks. For anemia, PAR/RIT + OMB + DAS + RBV for 12 weeks was less favourable than PAR/RIT + OMB + DAS for 12 weeks and LDV + SOF for 12 weeks. Evidence was limited for depression in treatment-experienced patients. There was insufficient evidence to include DCV + SOF in the analyses of these adverse events for treatment-experienced patients.

Economic Evidence

The cost-utility analysis of drugs for CHC infection was performed using an updated version of the model used for the 2014 CADTH Therapeutic Review of treatments for CHC infection.[14] The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY (ICUR). Of the treatment regimens that met the inclusion criteria of the protocol for the clinical review, only those treatments with price information available at the time of analysis were included in the base-case cost-utility analysis. DCV and asunaprevir (ASU) were included in exploratory analyses as they had been submitted to CDR at the time of analysis, but there were no publicly available prices for these agents. Various price scenarios were therefore modelled and are presented in the draft cost-effectiveness report[9] posted for stakeholder

consultation. However, since posting of this report, the manufacturer has provided the list price for DCV and the analyses were re-run using this price for CDEC deliberation. During the course of the Therapeutic Review, the CDR review of ASU was suspended and this agent has not yet received Health Canada approval. Cost-effectiveness results for this agent were therefore not considered by CDEC in developing recommendations.

Treatment effect estimates for SVR and adverse events (anemia, depression, and rash) were obtained from the CADTH systematic review and NMA. Other inputs for the economic model were derived from published sources and validated by clinical experts. Drug costs were obtained from the Ontario Drug Benefit Exceptional Access Program, Yukon Drug Formulary, the Saskatchewan Drug Plan, or directly from manufacturers. Extensive sensitivity analyses were conducted to test the effect of changes in underlying parameter values (parameter uncertainty) and assumptions within the models (structural uncertainty).

Genotype 1

The results of the base-case analysis suggest that for each genotype 1 population (treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic, or treatment-experienced cirrhotic), at least one of the interferon-free therapies appears to be economically attractive compared with PR alone (ICURs less than $30,000 per QALY). The drug that is most cost-effective varied by population, but was generally consistent across fibrosis stages.

For patients with genotype 1 CHC infection who are treatment-naive and non-cirrhotic, at a willingness to pay (λ) of $50,000 per QALY, PAR/RIT + OMB + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, LDV + SOF for 12 weeks was likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are treatment-experienced and non-cirrhotic, PAR/RIT + OMB + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone at a willingness to pay of $50,000 per QALY. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, RGT with SIM-PR was likely to be the most cost-effective option, followed by LDV + SOF + RBV for 12 weeks compared with PR alone. The incremental QALYs for PAR/RIT + OMB + DAS for 12 weeks and LDV + SOF for 12 weeks compared with PR were similar in all analyses.

A number of exploratory analyses were conducted for genotype 1 patients to reflect key sensitivity analyses performed as part of the NMAs for this population, as well as to account for DCV + SOF for 12 weeks, for which a publicly listed price was not available at the time of the original analysis:

- When including LDV + SOF for eight weeks in the analysis of patients who are treatment-naive without cirrhosis, this regimen was the most cost-effective option (ICUR $17,287 per QALY).
- When PAR/RIT + OMB + DAS + RBV for 12 weeks was included for patients with cirrhosis, it was the most cost-effective option for both treatment-naive and -experienced patients (ICUR $23,047 per QALY).
- When DCV + SOF for 12 weeks was considered for treatment-naive patients without cirrhosis, it was dominated by both PAR/RIT + OMB + DAS for 12 weeks and LDV + SOF for 12 weeks; however, the incremental QALYs when compared with PR were similar for all three regimens.

Genotype 2

For patients with genotype 2 CHC infection, who are treatment-naive and non-cirrhotic, the interferon-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis and those who are treatment-experienced without cirrhosis, SOF + RBV for 12 weeks was the most cost-effective option, with an ICUR of less than $60,000 per QALY (versus PR for treatment-naive patients, and versus no treatment for treatment-experienced patients). For patients who are treatment-experienced with cirrhosis, SOF + PR for 12 weeks was the most cost-effective option when compared with no treatment (ICUR of $18,226 per QALY), but it is currently not approved for this population; SOF + RBV for 12 weeks was the most cost-effective option that is approved in Canada (ICUR $21,338 per QALY).

Genotype 3

In the base-case analysis for genotype 3 infection, the interferon-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone for treatment-naive patients without cirrhosis (ICURs exceeded $150,000 per QALY). In patients who are treatment-naive with cirrhosis, SOF + RBV for 24 weeks was the most cost-effective approved option at an ICUR of $92,117 when compared with PR for 48 weeks. For patients who are treatment-experienced with or without cirrhosis, SOF + RBV for 24 weeks was the most cost-effective approved option (ICUR approximately $40,000 per QALY compared with no treatment). In exploratory analyses where DCV + SOF for 12 weeks was included in analyses of patients without cirrhosis regardless of treatment experience, this regimen was the most cost-effective among the approved regimens (ICURs $28,151 and $97,158 per QALY for treatment-experienced and -naive patients, respectively). However, the unapproved regimen SOF + PR for 12 weeks was the most cost-effective regimen versus PR in treatment-naive patients with genotype 3 infection (ICUR $70,792 per QALY), and versus no treatment for treatment-experienced patients, regardless of cirrhosis status (ICURs for patients with and without cirrhosis < $21,000 per QALY). In relation to SOF + PR for 12 weeks, the most cost-effective approved treatments for genotype 3 infection were either associated with very high ICURs, or were dominated.

Genotype 4

In the base-case analysis for patients with genotype 4 infection who are treatment-naive, no DAA-based regimen was found to be cost-effective in patients without cirrhosis (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis or those who are treatment-experienced, SOF + RBV for 24 weeks was considered the most cost-effective treatment (ICUR less than $60,000 per QALY), but is not currently indicated. SOF + PR for 12 weeks, the only approved treatment for genotype 4 infection, was included in an exploratory analysis of treatment-naive, non-cirrhotic patients with genotype 4 infection; this regimen was associated with an ICUR of $63,421 per QALY compared with PR.

Sensitivity and Scenario Analyses

In analyses stratified by fibrosis stage, ICURs for the interferon-free regimens compared with PR alone tended to be lower (more cost-effective) in patients with advanced fibrosis (F3) compared with patients with no or mild fibrosis (F0 to F2).

Extensive sensitivity analyses were conducted around the model input parameters, and the structural uncertainty was tested. Besides treatment efficacy, the main factors affecting the cost-effectiveness of the new interferon-free or the PR-based DAAs regimens versus PR alone were baseline age and the cost of antiviral therapies. The analyses showed that ICURs of interferon-

free or the PR-based DAAs therapies compared with PR tended to be lower (i.e., interferon-free or the PR-based DAAs are more cost-effective) in younger patients. Results of both the multiple one-way sensitivity analyses and probabilistic sensitivity analysis provide evidence that the most cost-effective alternatives for each population are likely to remain most cost-effective despite the various sources of uncertainty in the model parameters.

Due to the lack of sufficient data, no cost-effectiveness analyses could be performed for patients with genotype 5 or 6 infection, patients coinfected with HIV, or patients with liver transplant.

Members of the CADTH Canadian Drug Expert Committee

Dr. Lindsay Nicolle (Chair), Dr. James Silvius, (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets: None

Conflicts of Interest: None

External Clinical Experts

Two external clinical experts in hepatology attended the August 2015 CDEC meeting and participated in the discussion but did not vote on the draft recommendations.

About This Document

The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members.

The CDEC Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government, or the manufacturer.

Production of this report is made possible through a financial contribution from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

Cite as: Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review: recommendations report. Drugs for chronic hepatitis C infection [Internet]. Ottawa: The Agency; 2015 Nov. (CADTH therapeutic review). [cited yyyy mmm dd].

References

1. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007: final report [Internet]. Ottawa: Public Health Agency of Canada; 2009. [cited 2015 Jul 8]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf
2. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C virus infection in Canada. Can J Gastroenterol Hepatol. 2014 May;28(5):243-50.
3. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Rep [Internet]. 2013 Nov 20 [cited 2015 Jul 8];24(11):3-13. Available from: http://www.statcan.gc.ca/pub/82-003-x/2013011/article/11876-eng.pdf
4. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology [Internet]. 2013 Jun [cited 2015 Jan 29];57(6):2164-70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3763475
5. Al Naamani K, Al Sinani S, Deschenes M. Epidemiology and treatment of hepatitis C genotypes 5 and 6. Can J Gastroenterol [Internet]. 2013 Jan [cited 2015 Jan 29];27(1):e8-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3545628
6. Pawlotsky JM. Hepatitis C virus: standard-of-care treatment. Adv Pharmacol. 2013;67:169-215.
7. Welsch C, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. Gut. 2012 May;61 Suppl 1:i36-i46.
8. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review [draft for consultation]. Drugs for chronic hepatitis C infection: clinical review [Internet]. Ottawa: The Agency; 2015 Jul. [cited 2015 Sep 15]. Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Hep_C_Clinical_Report_Draft.pdf
9. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review [draft for consultation]. Drugs for chronic hepatitis C infection -- cost-effectiveness analysis [Internet]. Ottawa: The Agency; 2015 Jul. [cited 2015 Sep 15]. Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Hep_C_PE_Report.pdf
10. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Drugs for chronic hepatitis C infection: patient input information [Internet]. Ottawa: The Agency; 2015 Jul. [cited 2015 Sep 15]. Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Hep_C_Patient_Input_Summary.pdf
11. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol [Internet]. 2015 Jan [cited 2015 Aug 25];29(1):19-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334064
12. Hepatitis C treatments Viekira Pak and Technivie: drug safety communication - risk of serious liver injury [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 Oct 22. [cited 2015 Oct 26]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm468757.htm
13. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015 Sep;149(3):649-59.
14. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Direct-acting antiviral agents for chronic hepatitis C genotype 1 [Internet]. Ottawa: The Agency; 2014 Oct. [cited 2015 Apr 7]. (CADTH therapeutic review vol. 2, no. 2b). Available from: http://www.cadth.ca/media/pdf/TR0007_HepC_ScienceReport_e.pdf