CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

LEDIPASVIR/SOFOSBUVIR
(Harvoni — Gilead Sciences Canada, Inc.)
Indication: Chronic Hepatitis C Virus Genotype 1 Infection in Adults

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated March 18, 2015.

Recommendation:
CDEC recommends that ledipasvir/sofosbuvir (LDV/SOF) be reimbursed for the treatment of chronic hepatitis C virus (CHC) genotype 1 infection in adults, if the following conditions are met:

Conditions:
- Treatment should be initiated by physicians with experience in the management of CHC patients.
- Drug plan costs for LDV/SOF should not exceed the drug plan costs of other interferon (IFN)-free regimens for the treatment of CHC.

Reasons for the Recommendation:
1. Three randomized controlled trials (RCTs) (ION-1, ION-2, and ION-3) demonstrated that treatment with LDV/SOF with or without ribavirin (RBV) achieved high rates of sustained virologic response (SVR) at 12 weeks (SVR 12) for both treatment-naive and treatment-experienced patients with genotype 1 CHC infection.
2. At the submitted price ([redacted] per tablet containing 90 mg LDV and 400 mg SOF), LDV/SOF is considered to be a cost-effective treatment option compared with SOF or simeprevir (SIM) in combination with pegylated interferon and ribavirin (PR) for treatment-naive patients and treatment-experienced patients without cirrhosis. However, jurisdictions will need to consider drug plan and health care system sustainability when making listing decisions for the treatment of CHC infection with the newly available, costly treatment regimens.
3. Due to insufficient clinical evidence and limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of LDV/SOF according to liver fibrosis stage; however, CADTH's cost-effectiveness analysis in the Therapeutic Review *Drugs for Chronic Hepatitis C Infection* demonstrated that treatment of CHC is likely cost-effective across all Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scores

based on generally accepted thresholds. 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:

- CDEC noted that the 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.
- 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.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of LDV/SOF with other direct-acting antiviral (DAA) treatment regimens for CHC.
- The pharmacoeconomic consequences of reinfection following treatment with LDV/SOF or other treatment regimens for CHC require further evaluation.

Other Discussion Points:

CDEC noted the following:

- Therapy involving PR is associated with significant adverse events.
- Patients coinfected with hepatitis C virus (HCV) and HIV were excluded from ION-1, ION-2, and ION-3; however, data from a recently completed single-group trial (ERADICATE; N = 50) demonstrated similar SVR 12 rates (98%) in patients coinfected with HCV and HIV to those reported in the three pivotal trials.
- Patient groups indicated that those with CHC infection would like to have access to LDV/SOF irrespective of fibrosis stage, as they believe that the earlier the treatment is initiated, the more effective it is, and because they would like to be free of HCV as early as possible. CDEC considered this perspective; however, there is insufficient evidence to evaluate the clinical benefit and cost-effectiveness of treating patients with lower fibrosis stage levels.

Background:

LDV/SOF is the first product approved in Canada for the treatment of CHC genotype 1 that does not include PR. SOF is a nucleotide polymerase inhibitor and was the first DAA drug against the HCV to act on a target other than the protease. LDV is a new drug with a novel mechanism of action involving inhibition of non-structural protein A (NS5A), which is an essential component of HCV replicase. LDV/SOF is available as a single fixed-dose tablet containing 90 mg LDV and 400 mg SOF. It is administered orally once daily for 8 to 24 weeks, with duration determined by prior treatment experience and the presence of cirrhosis:

- 12 weeks for treatment-naive genotype 1 patients with or without cirrhosis and treatment-experienced patients without cirrhosis
- 24 weeks for treatment-experienced genotype 1 patients with cirrhosis

- a duration of 8 weeks for treatment-naive patients can be considered if the pre-treatment HCV viral load is less than 6 million IU/mL.

The product monograph states that the safety and efficacy of LDV/SOF have not been established in patients with decompensated cirrhosis.

Submission History:
In March 2015, CDEC recommended LDV/SOF be listed for the treatment of CHC genotype 1 infection in adults, if the following clinical criterion and conditions are met:

Clinical criterion:
- Liver fibrosis stage ≥ 2.

Conditions:
- Treatment should be initiated by physicians with experience in the management of patients with CHC infection.
- Substantial reduction in price

As part of the CADTH Therapeutic Review (*Drugs for Chronic Hepatitis C Infection*), CDEC issued evidence-informed recommendations in November 2015 to address the optimal use of all currently available interferon (IFN)-free treatments for CHC infection for multiple genotypes.

1. 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.
2. LDV/SOF and OMB/PAR/RIT + DAS ± RBV as preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status.
3. The following are preferred regimens for patients with CHC infection genotypes 2 through 4:
   - genotype 2: SOF + RBV for 12 weeks
   - genotype 3 without cirrhosis: DCV + SOF for 12 weeks
   - genotype 3 with cirrhosis: SOF + RBV for 24 weeks
   - genotype 4 treatment-naive without cirrhosis: SOF + PR for 12 weeks.
4. CDEC considered there to be insufficient evidence to make a recommendation for patients with genotype 4 CHC who are treatment-experienced or with cirrhosis regardless of treatment experience, genotype 5 CHC, and genotype 6 CHC.

The CADTH Common Drug Review (CDR)-participating jurisdictions submitted a request for advice to ask CDEC if the recommendation for LDV/SOF should be updated to align with the CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*?

Summary of CDEC Considerations:
CDEC considered the following to address the request for advice:
- Materials included in the CDEC brief for the 2015 CDR review of LDV/SOF.
- The 2015 CDEC recommendation for LDV/SOF (March 18, 2015).
- The CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*.

- The CDR request for advice brief, which included a detailed comparison of the key reasons and evidence underlying the CDEC recommendation for LDV/SOF and the CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*.
- Input from five patient groups which described the impacts of hepatitis C infection and expectations from therapy.

Comparison of CDEC Recommendations:
The primary difference between CDEC's recommendation from the individual review of LDV/SOF and the recommendations from the therapeutic review is the presence or absence of a clinical criterion related to liver fibrosis staging. The CDEC recommendation for LDV/SOF included a clinical criterion that treatment should only be provided for patients with a liver fibrosis stage of ≥ 2. The rationale for this criterion was stated as follows: *Due to insufficient clinical evidence and limitations of the manufacturer's pharmacoeconomic model, CDEC was unable to evaluate the cost-effectiveness of LDV/SOF according to liver fibrosis stage, particularly for patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).*

In contrast to the initial CDEC recommendation for LDV/SOF, when considering the findings of CADTH's therapeutic review, CDEC recommended LDV/SOF and OMB/PAR/RIT + DAS ± RBV as the preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status or fibrosis score. In the reasons for the therapeutic review recommendations, CDEC noted that CADTH's cost-effectiveness analysis demonstrated that treatment of CHC is likely cost-effective across all METAVIR scores based on generally accepted thresholds.

Summary of Patient Input for the Current Request for Advice:
Five patient groups, the Canadian Liver Foundation, Action Hepatitis Canada, the Pacific Hepatitis C Network, the Canadian Treatment Action Council (CTAC), and the HepCBC Hepatitis C Education and Prevention Society responded to the CDR call for patient input.

- Patient groups supported that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. It was acknowledged that, should drug plans be unable to provide coverage for all patients, priority should be given to those with more severe disease.
- In general, patients are willing to tolerate treatment with ribavirin in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with ribavirin are much less severe than those associated with pegylated interferon.

Evidence from the CDR Review of LDV/SOF:

Patient Input Information
The following is a summary of information provided by five patient groups that responded to the CDR call for patient input:

- CHC infection is a serious and potentially life-threatening disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and death. Patients may experience fatigue; general weakness; abdominal, muscle or joint pain; itchiness; poor circulation; constipation; nausea; loss of appetite; headaches; disrupted sleep; and jaundice. Cognitive functioning is affected in some patients.

- Patients must cope with the stigma associated with CHC infection and are often reluctant to disclose their HCV status for fear of rejection and discrimination.
- Spouses and loved ones who care for patients with CHC infection are faced with a substantial burden, as the symptoms of the infection and side effects of treatment can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children.
- Current therapy is limited by adverse effects that can be debilitating. In addition, some treatment regimens may require patients to take up to 20 pills throughout the day.
- The expectations for LDV/SOF are that it will address a large gap in current care and unmet patient needs. There is currently no treatment available for patients with a null response or relapse to standard therapies. Due to its low toxicity and lack of drug interactions, it is expected that LDV/SOF will open up treatment to patients who had contraindications to, or who could not tolerate, IFN-based treatments. Patients see advantages with LDV/SOF that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients, higher response rates.

Clinical Trials

The CDR systematic review included three pivotal phase 3 RCTs (ION-1, ION-2, and ION-3). All trials were multi-group open-label RCTs designed to assess various durations of LDV/SOF 90 mg/400 mg with or without RBV in patients with genotype 1 CHC infection. ION-1 (N = 870) was a four-group, open-label trial in treatment-naive patients: LDV/SOF for 12 weeks, with or without RBV, and LDV/SOF for 24 weeks, with or without RBV. ION-3 (N = 647) was a three-group trial that assessed LDV/SOF for eight weeks, with or without RBV, and LDV/SOF for 12 weeks, in treatment-naive patients with CHC genotype 1 infection. ION-2 (N = 441) had the same treatment groups as ION-1, but enrolled treatment-experienced patients with CHC genotype 1 infection who had had either a relapse or non-response to an interferon-based regimen (including regimens containing NS3/4A protease inhibitors). ION-1 and ION-2 both allowed enrolment of up to 20% of the patients with confirmed cirrhosis, while ION-3 excluded patients with cirrhosis. In other respects, all three trials had similar inclusion and exclusion criteria. Patients with significant comorbidities or other active clinical conditions commonly seen in the CHC infection population, most notably hepatitis B and HIV co-infection, were excluded in all trials.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- SVR 12 — defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) 12 weeks after stopping all study drugs.
- Relapse — defined as having HCV RNA greater than or equal to LLOQ during the post-treatment period after having achieved HCV RNA less than LLOQ at the end of treatment, confirmed with two consecutive values or last available post-treatment measurement.
- SF-36 — a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems. SF-36 also provides two component summaries, the physical component summary and the mental component summary.

- Chronic Liver Disease Questionnaire (CLDQ) — an instrument used to assess the health-related quality of life for patients with chronic liver disease. CLDQ measures activity/energy, emotion, worry, and systemic symptoms, which are combined in the CLDQ total score. All domains and the total score are based on a Likert scale of 0 (worst) to 7 (best).
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale — a 40-item scale used to assess fatigue and the impact of fatigue on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale, make up the total score ranging from 0 (worst) to 160 (best).
- Work Productivity and Activity Impairment questionnaire — an instrument used to measure the impact of a disease on work and on daily activities.

The primary outcome of all studies was the proportion of patients with SVR 12.

Efficacy

- All treatment groups were statistically significantly superior to the historical control rates for SVR 12 ($P < 0.001$). The proportion of patients with SVR 12 was reported as follows:
  - ION-1: 99% for LDV/SOF (12 weeks), 97% for LDV/SOF + RBV (12 weeks), 98% for LDV/SOF (24 weeks), and 99% for LDV/SOF + RBV (24 weeks) versus 60% historical control rate
  - ION-2: 93.6% for LDV/SOF (12 weeks), 96.4% for LDV/SOF + RBV (12 weeks), 99.1% for LDV/SOF (24 weeks), and 99.1% for LDV/SOF + RBV (24 weeks) versus 25% historical control rate
  - ION-3: 94% for LDV/SOF (8 weeks), 93.1% for LDV/SOF + RBV (8 weeks), and 95.4% for LDV/SOF (12 weeks) versus 60% historical control rate
  - As a secondary analysis, both LDV/SOF and LDV/SOF + RBV for 8 weeks were non-inferior to LDV/SOF for 12 weeks (based on a non-inferiority margin of 12%).
- The proportion of patients experiencing relapse was reported as follows:
  - ION-1: 0.5% in both the LDV/SOF (12 weeks) and LDV/SOF (24 weeks) groups
  - ION-2: 6.5% for LDV/SOF (12 weeks), 3.6% for LDV/SOF + RBV (12 weeks), 0% in both of the 24-week treatment groups
  - ION-3: 5.1% for LDV/SOF (8 weeks), 4.2% for LDV/SOF + RBV (8 weeks) and 1.4% for LDV/SOF (12 weeks).
- Changes in SF-36, CLDQ-HCV, and FACIT-F scores from baseline to the end of treatment were modest and typically showed improvement from baseline; however, there were no comparisons made between treatment groups.

Harms (Safety and Tolerability)

- The most common adverse events reported for LDV/SOF regimens included fatigue, headache, and nausea (all > 10%). When RBV was combined with LDV/SOF, the regimen was associated with higher rates of cough, pruritus, rash, insomnia, irritability, and anemia than those that did not contain RBV.
- The proportion of patients who experienced at least one adverse event was reported as follows:
  - ION-1: 78.5% for LDV/SOF (12 weeks), 84.8% for LDV/SOF + RBV (12 weeks), 81.6% for LDV/SOF (24 weeks), and 92.2% for LDV/SOF + RBV (24 weeks)

  - ION-2: 67% for LDV/SOF (12 weeks), 86.5% for LDV/SOF + RBV (12 weeks), 80.7% for LDV/SOF (24 weeks), and 90.1% for LDV/SOF + RBV (24 weeks)
  - ION-3: 67.4% for SOF/LDV (8 weeks), 76.4% for LDV/SOF + RBV (8 weeks), and 69% for SOF/LDV (12 weeks).
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - ION-1: 0.5% for LDV/SOF (12 weeks), 3.2% for LDV/SOF + RBV (12 weeks), 8.3% for LDV/SOF (24 weeks), and 2.8% for LDV/SOF + RBV (24 weeks)
  - ION-2: No patients in the 12-week treatment groups, 5.5% for LDV/SOF (24 weeks), and 2.7% for LDV/SOF + RBV (24 weeks)
  - ION-3: 1.9% for LDV/SOF (8 weeks), 0.5% for LDV/SOF + RBV (8 weeks), and 2.3% for LDV/SOF (12 weeks).
- The proportion of patients who experienced an adverse event leading to discontinuation of any study drug was reported as follows:
  - ION-1: 0% for LDV/SOF (12 weeks), 0.5% for LDV/SOF + RBV (12 weeks), 1.8% for LDV/SOF (24 weeks), and 3.7% for LDV/SOF + RBV (24 weeks)
  - ION-2: 0% (no patients) in any treatment group
  - ION-3: 0% for LDV/SOF (8 weeks), 0.9% for LDV/SOF + RBV (8 weeks), and 0.9% for LDV/SOF (12 weeks).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis over a lifetime horizon (up to 80 years of age) comparing LDV/SOF with SOF + PR, SIM + PR, telaprevir + PR, boceprevir + PR, SOF + RBV, and no treatment from a public-payer perspective, in patients with genotype 1 CHC. The model included nine health states: two states representing the non-cirrhotic disease (CHC non-cirrhotic and SVR non-cirrhotic), three states representing cirrhotic disease (compensated cirrhosis, decompensated cirrhosis, and SVR cirrhotic), hepatocellular carcinoma, liver transplant, post-liver transplant, and death. The cohort consisted of a mixture of cirrhotic and non-cirrhotic patients, and separate analyses were conducted for treatment-naive patients, treatment-experienced patients, and patients who had failed treatment with a protease inhibitor.

Natural history transition rates were based on a number of different published studies, including Grishchenko et al. The clinical effectiveness data were taken from the active groups of the pivotal trials for the therapies being evaluated (i.e., a naive indirect comparison). For patients with prior failure to a protease inhibitor, SVR rates from the subgroup of patients experienced with a protease inhibitor in ION-2 and an abstract from Pol et al. were used for LDV/SOF and SOF + PR, respectively. In an alternate analysis, results from a manufacturer-conducted network meta-analysis were used to inform comparative effectiveness in treatment-naive patients. Utility data (Health Utilities Index Mark 2 [HUI2] and Mark 3 [HUI3]) were taken from two surveys of a Canadian CHC population (Hsu 2012 and John-Baptiste 2009). Resource utilization was based on clinical trial observations, clinical experts' assumptions, and the literature. Costs were taken from Ontario health care cost sources. The model did not have states for screening and diagnosis, or a reinfection state. The model did not allow an assessment of the cost-effectiveness of 12 weeks LDV/SOF compared with 8 weeks LDV/SOF in treatment-naive non-cirrhotic patients.

In the base-case analyses, the manufacturer reported that LDV/SOF was dominant compared with active comparators for treatment-naive patients, and associated with an incremental cost-

utility ratio (ICUR) of $17,928 per quality-adjusted life-year (QALY) gained, compared with no treatment. For treatment-experienced patients, LDV/SOF dominated SOF + RBV and ICURs for LDV/SOF compared with all other comparators were less than $30,000 per QALY. For patients who failed protease inhibitors, the ICURs for LDV/SOF were less than $30,000 per QALY compared with SOF + PR and with no treatment.

CDR identified several limitations with the submitted pharmacoeconomic model:

- The clinical effectiveness parameters used in the model were drawn from non-comparative trials.
- The model structure aggregated fibrosis stages in early disease (F0, F1, F2, and F3) that have very different costs of care. This artificially increases the expected value of eliminating the virus.
- Natural history data for non-cirrhotic to cirrhotic transition appear to be erroneous.
- The cost of anemia was likely overestimated, which would overestimate total cost of comparators and favour LDV/SOF.
- The duration of PR therapy with the SIM + PR regimen was underestimated, which would overestimate the cost of SIM + PR and favour LDV/SOF.
- The utility parameters might not be reliable.

CDR conducted a number of reanalyses, using lower anemia costs, shorter duration of PR in the SIM + PR regimen, and alternate utility values, but was not able to account for all identified limitations, as many of them were related to structural problems with the model or fundamental problems with the evidence base. Therefore, there remains considerable uncertainty in the results:

- In treatment-naive and treatment-experienced non-cirrhotic patients, LDV/SOF is likely to remain cost-effective versus active comparators; although on balance CDR considers that results generated by the model are likely to be an underestimate of the actual ICUR of LDV/SOF versus other comparators.
- In treatment-experienced cirrhotic patients, ICURs for LDV/SOF versus SOF + PR were consistently greater than $50,000 per QALY (with a less than 30% probability that the ICUR would be less than $50,000 per QALY), and the ICUR for LDV/SOF versus SIM + PR increased to $36,000 per QALY. The estimates of the cost-effectiveness of LDV/SOF in cirrhotic treatment-experienced patients are similarly limited by the flaws in the submitted model, and even the CDR analyses are likely to represent an underestimate of the actual ICUR in this group.

At the submitted price of [redacted] per day, for non-cirrhotic genotype 1 patients, an eight-week course of LDV/SOF ([redacted]) is less costly than SIM + PR regimens ($46,002 to $55,502) and less costly than a 12-week course of SOF + PR ([redacted], based on the confidential price submitted to CDR for sofosbuvir). A 12-week course of LDV/SOF ([redacted]) is more costly than SIM with a 24-week course of PR ($46,002) and more costly than a 12-week course of SOF + PR, [redacted] than SIM with a 48-week course of PR ($55,502). For treatment-experienced cirrhotic patients, the cost of a 24-week course of LDV/SOF ([redacted]) is more expensive than all other CHC regimens currently available.

Evidence from the CADTH Therapeutic Review:

Treatment-Naive Patients with Genotype 1 CHC

- For treatment-naive patients with genotype 1 CHC, all of the DAA treatment strategies under review, with the exception 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 OMB/PAR/RIT + DAS ± RBV for 12 weeks significantly improved SVR compared with SOF + RBV for 24 weeks, response-guided therapy with SIM + PR, and SOF + PR for 12 weeks (result was statistically non-significant for OMB/PAR/RIT + 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 OMB/PAR/RIT + 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 IFN-free regimens; there were no significant differences in SVR 12 among the following groups: LDV/SOF for 12 weeks, DCV + SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks where these regimens could be compared with one another.
- LDV/SOF for 12 weeks, OMB/PAR/RIT + 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 OMB/PAR/RIT + DAS for 12 weeks were significantly associated with less rash and depression compared with PR-based treatments. For rash, OMB/PAR/RIT + 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 any of the IFN-free regimens.
- For anemia, OMB/PAR/RIT + 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 OMB/PAR/RIT + DAS ± RBV for 12 weeks or LDV/SOF for 12 weeks on this outcome.

Treatment-Experienced Patients with Genotype 1 CHC

- All of the DAA treatment strategies significantly improved SVR compared with PR (RR ranged from 2.72 to 3.75). There were no significant differences found when LDV/SOF for 12 weeks was compared with OMB/PAR/RIT + 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 most subgroups when LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were compared against each other. One exception was the subgroup analysis of patients without cirrhosis, in which OMB/PAR/RIT + DAS + RBV 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 OMB/PAR/RIT + 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 a of data. As well, analysis by type of prior response was not possible for IFN-free regimens in patients with cirrhosis, due to a lack of data.
- LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV/SOF for 12 weeks and

OMB/PAR/RIT + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments.
- For rash there was no significant difference between OMB/PAR/RIT + DAS ± RBV for 12 weeks and LDV/SOF for 12 weeks.
- For anemia, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks.

Cost-Effectiveness

CADTH conducted a cost-utility analysis of drugs for CHC infection employing an updated version of the model used for the 2014 CADTH therapeutic review of treatments for CHC infection. The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY (ICUR). Treatment effect estimates for SVR and adverse events (anemia, depression, and rash) were obtained from the CADTH systematic review and network meta-analysis. 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.

The base-case analysis suggested that for each genotype 1 population (i.e., treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic, or treatment-experienced cirrhotic), at least one of the IFN-free therapies appeared 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, OMB/PAR/RIT + 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, OMB/PAR/RIT + 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, response-guided therapy 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 OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks compared with PR were similar in all analyses.

CDEC Members:

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.

April 20, 2016 Meeting
Regrets:

One CDEC member was unable to participate in this portion of the meeting.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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