CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DACLATASVIR
(Daklinza — Bristol-Myers Squibb Canada Inc.)
Indication: Chronic Hepatitis C Genotype 1, 2, or 3 Infection in Adults

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated September 21, 2015.

Recommendation:
CDEC recommends that daclatasvir (DCV), in combination with sofosbuvir (SOF), be reimbursed for the treatment of patients with genotype 3 chronic hepatitis C (CHC), if the following clinical criterion and conditions are met:

Clinical criterion:
- Patient does not have cirrhosis.

Conditions:
- Prescribing restricted to hepatologists and physicians with experience treating patients with CHC.
- Drug plan cost of a treatment course with DCV/SOF should not exceed the drug plan cost of a treatment course with SOF plus ribavirin (SOF/RBV).
- Duration of treatment with DCV/SOF should be limited to 12 weeks.

Reasons for the Recommendation:

1. One open-label, uncontrolled study (ALLY-3) demonstrated that a subgroup of treatment-experienced patients with genotype 3 CHC who were treated with DCV/SOF for 12 weeks had high rates of sustained virologic response (SVR 12) (86%; 95% confidence interval, 74% to 94%).
2. Patients with genotype 3 CHC and cirrhosis showed relatively low rates of SVR 12 (58% to 69%) in ALLY-3. Due to the lack of clinical data, CADTH was unable to incorporate the DCV/SOF for 12 weeks regimen into the therapeutic review (TR) analysis of genotype 3 patients with cirrhosis.
3. Reanalyses of the manufacturer's pharmacoeconomic evaluation and CADTH's pharmacoeconomic analysis demonstrated that treatment with DCV/SOF was cost-effective

compared with 24 weeks of SOF/RBV when used in patients with genotype 3 CHC without cirrhosis.

4. CADTH's cost-effectiveness analysis in the Therapeutic Review of *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 manufacturer's requested listing criteria for DCV/SOF were limited to patients with genotype 3 CHC.
- 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. Extra-hepatic 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 DCV/SOF versus other DAA regimens or combinations that are currently used in Canada.
- There are limited data on patients who failed previous DAA treatments, patients with cirrhosis, and patients with comorbidities.

Other Discussion Points:

CDEC noted the following:

- Patient groups would like effective treatment options for CHC that do not involve the use of interferon (IFN) and/or RBV, both of which are associated with significant adverse effects. DCV/SOF is an IFN-free regimen for the treatment of genotype 3 CHC that does not require concomitant use of RBV when administered in non-cirrhotic patients.
- The quality of evidence from ALLY-3 and study 040 is limited by small sample sizes, open-label administration of the study drugs, and the lack of a control group. However, the study design was relatively consistent with the design of clinical trials used in other DAAs for the treatment of CHC.

Background:

DCV, a direct-acting antiviral (DAA) drug against the hepatitis C virus (HCV), is a highly selective inhibitor of the HCV nonstructural protein 5A (NS5A) replication complex. DCV has a Health Canada indication for use in combination with other drugs for the treatment of CHC infection in adults with HCV genotype 1, 2, or 3 infection and compensated liver disease (including cirrhosis). Health Canada issued marketing authorization with conditions for DCV patients with genotype 3 HCV infection, pending the results of a trial to verify its clinical benefit.

DCV is available as 30 mg and 60 mg tablets. The recommended dose is 60 mg once daily in combination with SOF for 12 or 24 weeks, with the duration determined by the HCV genotype, prior treatment experience, and the presence of cirrhosis:

- 12 weeks for genotype 1 or 3 (treatment-naive or experienced) without cirrhosis
- 24 weeks for genotype 1 or 3 (treatment-naive or experienced) with cirrhosis
- 24 weeks for genotype 2 (treatment-naive) with or without cirrhosis
- 24 weeks for genotype 2 (treatment-experienced) without cirrhosis.

The addition of RBV can be considered for patients with genotype 2 or 3 HCV and compensated cirrhosis. The product monograph states that the safety and efficacy of DCV have not been established in patients with decompensated cirrhosis.

Submission History:
In September 2015, CDEC recommended that DCV/SOF be listed for the treatment of patients with genotype 3 CHC, if the following clinical criterion and conditions are met:

Clinical criterion:

- Treatment-experienced patients without cirrhosis who have not responded to PR.

Conditions:

- Prescribing restricted to hepatologists and physicians with experience treating patients with CHC.
- Drug plan cost of a treatment course with DCV/SOF should not exceed the drug plan cost of a treatment course with SOF/RBV.

This review was based on the Health Canada approved indication for which the Notice of Compliance was issued on August 13, 2015.

As part of a 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 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 DCV/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 DCV/SOF.
- The CDEC recommendation for DCV/SOF (September 21, 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 DCV/SOF and the CDEC recommendations from the Therapeutic Review of *Drugs for Chronic Hepatitis C Infection*.
- Input from five patient groups, which described the impact of hepatitis C infection and expectations from therapy.

Comparison of CDEC Recommendations:
The primary difference between CDEC's recommendation from the individual review of DCV/SOF and the recommendations from the TR is the inclusion or exclusion of treatment-naive patients without cirrhosis. The CDEC recommendation from the individual CDR review for DCV/SOF included a clinical criterion that is should be restricted to treatment-experienced patients with genotype 3 CHC, without cirrhosis, and who have not responded to PR. The rationale for this criterion was stated as follows: *Reanalyses of the manufacturer's pharmacoeconomic evaluation demonstrated that treatment with DCV/SOF was cost-effective compared with 24 weeks of SOF/RBV when used in patients with genotype 3 CHC who are treatment-experienced without cirrhosis. However, DCV/SOF was not considered to be a cost-effective option for use in patients with genotype 3 CHC who are treatment-naive and/or have cirrhosis.*

In contrast to the initial CDEC recommendation for DCV/SOF, when considering the findings of CADTH's TR, CDEC recommended DCV/SOF as the preferred regimen for patients with CHC genotype 3 infection without cirrhosis who are treatment-naive or PR-experienced. In consideration of the evidence from the TR, CDEC gave considerable weight to input from patient groups and clinical experts who suggested that pegylated-interferon (Peg-IFN) should be avoided, whenever possible, due to its adverse effect profile. Therefore, CDEC recommended the most cost-effective Peg-IFN-free regimens.

CDEC noted the following in support of the recommendation that DCV/SOF is the preferred option for patients with genotype 3 CHC infection without cirrhosis (regardless of treatment experience): *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.*

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 RBV in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with RBV are much less severe than those associated with Peg-IFN.

Evidence from the CDR Review of DCV/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.
- The expectations for DCV are that it will address unmet patient needs. Due to its low toxicity and lack of drug interactions, it is expected that DCV will open up treatment to patients who had contraindications to, or who could not tolerate, IFN-based treatments. Patients see advantages with DCV that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients, high response rates.

Clinical Trials
The systematic review included two open-label, uncontrolled trials in patients with genotype 3 (ALLY-3) or genotype 1, 2, or 3 CHC (study 040) and included both treatment-naive and treatment-experienced cohorts. DCV was combined with SOF for 12 weeks (ALLY-3, 040) or 24 weeks (study 040) with and without RBV. The sample size per treatment cohort ranged from 14 to 101 patients. All trials excluded patients with decompensated liver disease, hepatitis B or HIV co-infection, malignancy, or recent substance abuse.

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.
- EuroQoL 5-Dimensions Questionnaire (EQ-5D) — 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. EQ-5D consists of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) that are converted to a utility score.

The primary outcome in both trials was the proportion of patients who achieved SVR 12.

Efficacy

- Among patients who received DCV/SOF, the proportion of patients with SVR 12 was reported as follows:
  - Study 040: genotype 1 treatment-naive 100% (12 weeks); 100% (24 weeks)
  - Study 040: genotype 1 treatment-experienced 100% (24 weeks)
  - Study 040: genotype 2 or 3 treatment-naive 100% (24 weeks)
  - ALLY-3: genotype 3 treatment-naive 90% (12 weeks)
  - ALLY-3: genotype 3 treatment-experienced 86% (12 weeks).
- In ALLY-3, patients with cirrhosis had a lower SVR 12 rate (58% to 69%, total N = 29) than those without cirrhosis (94% to 97%, total N = 109).
- Among patients who received DCV/SOF + RBV, the proportion of patients with SVR 12 was reported as follows:
  - Study 040: genotype 2 or 3 treatment-naive 86% (24 weeks).
- Relapse was reported in 9% of treatment-naive and 14% of treatment-experienced genotype 3 patients in ALLY-3. No relapses were reported in Study 040.
- In ALLY-3, no clinically important changes in quality of life scores were observed at the end of treatment, or 12 weeks after treatment, in patients who received DCV/SOF for 12 weeks.

Harms (Safety and Tolerability)

- The most commonly reported adverse events for DCV/SOF regimens included headache (20% to 34%), nausea (0% to 36%), and fatigue (14% to 50%). The proportion of patients who experienced at least one adverse event was reported as follows:
  - ALLY-3: 66% to 78% (12 weeks)
  - Study 040: 93% (12 weeks); 76% to 93% (24 weeks).
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - ALLY-3: 0% to 1% (12 weeks)
  - Study 040: 2% (12 weeks); 0% to 14% (24 weeks).
- The proportion of patients who experienced an adverse event leading to discontinuation of any study drug was reported as follows:
  - ALLY-3: 0% (12 weeks)
  - Study 040: 0% (12 weeks); 0% to 7% (24 weeks).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis assessing the cost-effectiveness of DCV/SOF in treatment-naive and treatment-experienced patients with various genotypes of HCV (genotype 1, 2, or 3) and either cirrhotic status (cirrhotic or non-cirrhotic). The comparators varied by genotypes and consisted of DAAs + PR regimens (SOF, simeprevir, telaprevir, and boceprevir), SOF/RBV, and PR alone over a lifetime horizon (up to 100 years of age) from a

Ministry of Health perspective. The submission used the Modelling the Natural History of Cost-effectiveness of Hepatitis (MONARCH) model that tracked patients through the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis states through to decompensated cirrhosis, complications (hepatocellular carcinoma, liver transplantation), and death. Where SVR was obtained, patients moved to a set of SVR-specific states in which relapse to HCV-positive states did not occur and progression was limited only to the case where SVR was obtained following existing compensated cirrhosis. The model did not allow for reinfection or relapse. Most of the model inputs (transition probabilities, utility data, disease-specific costs, costs of adverse events) were based on the 2014 CADTH Therapeutic Review *Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1,* which based its figures on Thein et al. (2008), Hsu et al. (2012), Krajden et al. (2010), and Gao et al. (2012). Drug costs were sourced from the DeltaPA database (IMS Brogan 2014).

The manufacturer reported that a 12-week treatment regimen of DCV/SOF in treatment-naive and treatment-experienced patients with genotype 3 and a fibrosis stage between F0 and F3 is dominant (i.e., less costly and more effective) compared with a 24-week regimen of SOF/RBV. However, in treatment-naive patients, SOF/RBV was not cost-effective versus PR. Given this, the manufacturer's claim of dominance in treatment-naive patients is possibly misleading.

CDR identified several limitations with the manufacturer's pharmacoeconomic submission:

- There is uncertainty with comparative SVR and adverse events rates for DCV/SOF versus comparators. The manufacturer used matching-adjusted indirect comparisons (genotype 1 treatment-naive, genotype 3) and naive indirect comparisons (genotype 2). In addition, comparative evidence in treatment-experienced patients was limited to genotype 3.
- The manufacturer's model does not allow a clear comparison of all comparators simultaneously.
- There is a lack of comparison with other available IFN-free regimens (for genotype 1 patients) and no treatment (for all genotypes).
- All-cause mortality risk was not correctly applied in patients with advanced disease, and the probabilistic sensitivity analysis did not adhere to best modelling practices.

CDR reanalyses applying a risk of all-cause mortality to advanced disease health states and modifying the probabilistic sensitivity analysis demonstrated that DCV/SOF did not appear economically attractive in any comparison, except in genotype 3 treatment-experienced patients without cirrhosis when compared with 24 weeks of SOF/RBV where DCV/SOF was dominant.

At the submitted price of [redacted] per tablet for DCV ([redacted] course of treatment), the DCV/SOF 12-week regimen is less costly than a 24-week course of SOF/ RBV ($113,045 to $117,308), but more costly than a 48-week course of PR ($9,437 to $20,855).

Evidence from the CADTH Therapeutic Review:

Efficacy and Safety

Treatment-naive Patients with Genotype 3 CHC

- 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.

- 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.
- For patients with cirrhosis, SOF/RBV for 24 weeks significantly improved SVR compared with PR for 48 weeks. There was no significant difference between SOF 12 + PR 12 and SOF/RBV for 24 weeks.
- For patients without cirrhosis, SOF/RBV for 24 weeks, DCV/SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR compared with PR alone for 48 weeks. There were no significant differences between these 3 regimens.
- 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 3 CHC

- 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.
- For patients with cirrhosis, SOF/RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR compared with PR for 48 weeks. There was no significant difference between SOF/RBV for 24 weeks and SOF + PR for 12 weeks.
- For patients without cirrhosis, SOF/RBV for 24 weeks, DCV/SOF for 12 weeks and SOF 12 + PR12 significantly improved SVR compared with PR for 48 weeks There was no significant differences between SOF 24 + RBV 24, DCV/SOF for 12 weeks, and SOF + PR for 12 weeks.
- 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 using 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 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.

In the base-case analysis for genotype 3 infection, the IFN-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.

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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