

CDEC FINAL RECOMMENDATION

DACLATASVIR

(Daklinza — Bristol-Myers Squibb Canada Inc.)

Indication: Chronic Hepatitis C Genotype 1, 2, or 3 Infection in Adults

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that daclatasvir, in combination with sofosbuvir, be listed for the treatment of patients with genotype 3 chronic hepatitis C (CHC), if the following clinical criterion and conditions are met:

Clinical criterion:

- Treatment-experienced patients without cirrhosis who have not responded to pegylated-interferon plus ribavirin (PR).

Conditions:

- Prescribing restricted to hepatologists and physicians with experience treating patients with CHC.
- Drug plan cost of a treatment course with daclatasvir plus sofosbuvir should not exceed the drug plan cost of a treatment course with sofosbuvir plus ribavirin.

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 daclatasvir plus sofosbuvir for 12 weeks had high rates of sustained virologic response (SVR12) (86%; 95% confidence interval, 74% to 94%).
2. Reanalyses of the manufacturer's pharmacoeconomic evaluation demonstrated that treatment with daclatasvir plus sofosbuvir was cost-effective compared with 24 weeks of sofosbuvir plus ribavirin when used in patients with genotype 3 CHC who are treatment-experienced without cirrhosis. However, daclatasvir plus sofosbuvir was not considered to be a cost-effective option for use in patients with genotype 3 CHC who are treatment-naïve and/or have cirrhosis.

Of Note:

- The manufacturer's requested listing criteria for daclatasvir plus sofosbuvir were limited to patients with genotype 3 CHC.
- The clinical criterion in this recommendation is not stating that treatment-naïve patients with genotype 3 CHC should be treated with PR as a first-line option.

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Background:

Daclatasvir, a direct-acting antiviral (DAA) agent against the hepatitis C virus (HCV), is a highly selective inhibitor of the HCV nonstructural protein 5A (NS5A) replication complex. Daclatasvir has a Health Canada indication for use in combination with other agents 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 daclatasvir patients with genotype 3 HCV infection, pending the results of a trial to verify its clinical benefit.

Daclatasvir is available as 30 mg and 60 mg tablets. The recommended dose is 60 mg once daily in combination with sofosbuvir 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-naïve or experienced) without cirrhosis
- 24 weeks for genotype 1 or 3 (treatment-naïve or experienced) with cirrhosis
- 24 weeks for genotype 2 (treatment-naïve) with or without cirrhosis
- 24 weeks for genotype 2 (treatment-experienced) without cirrhosis.

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

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of pivotal studies of daclatasvir plus sofosbuvir, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients with CHC.

Patient Input Information

The following is a summary of information provided by four 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 daclatasvir are that it will address unmet patient needs. Due to its low toxicity and lack of drug interactions, it is expected that daclatasvir will open up treatment to patients who had contraindications to, or who could not tolerate, interferon-based treatments. Patients see advantages with daclatasvir 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. Daclatasvir was combined with sofosbuvir for 12 weeks (ALLY-3, 040) or 24 weeks (study 040) with and without ribavirin. 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:

- SVR12 — 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 SVR12.

Efficacy

- Among patients who received daclatasvir plus sofosbuvir, the proportion of patients with SVR12 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 SVR12 rate (58% to 69%, total N = 29) than those without cirrhosis (94% to 97%, total N = 109).
- Among patients who received daclatasvir plus sofosbuvir and ribavirin, the proportion of patients with SVR12 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 daclatasvir plus sofosbuvir for 12 weeks.

Harms (Safety and Tolerability)

- The most commonly reported adverse events for daclatasvir plus sofosbuvir 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 daclatasvir plus sofosbuvir 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 (sofosbuvir, simeprevir, telaprevir, and boceprevir), sofosbuvir plus ribavirin, 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 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), Kraiden 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 daclatasvir plus sofosbuvir 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 sofosbuvir plus ribavirin. However, in treatment-naive patients, sofosbuvir plus ribavirin 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 daclatasvir plus sofosbuvir 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 interferon-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.

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

At the submitted price of \$ [REDACTED] per tablet for daclatasvir ([REDACTED]), the daclatasvir plus sofosbuvir 12-week regimen is less costly than a 24-week course of sofosbuvir plus ribavirin (\$113,045 to \$117,308), but more costly than a 48-week course of PR (\$9,437 to \$20,855).

Other Discussion Points:

CDEC noted the following:

- Patient groups would like effective treatment options for CHC that do not involve the use of interferon and/or ribavirin, both of which are associated with significant adverse effects. Daclatasvir plus sofosbuvir is an interferon-free regimen for the treatment of genotype 3 CHC that does not require concomitant use of ribavirin 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.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of daclatasvir plus sofosbuvir 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.

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 Wijeyesundera.

August 19, 2015 Meeting

Regrets:

None

Conflicts of Interest:

None

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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*.

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