CDEC FINAL RECOMMENDATION

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ledipasvir/sofosbuvir (LDV/SOF) be listed for the treatment of chronic hepatitis C virus (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

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 (SVR12) 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, particularly for patients without fibrosis or those with early-stage fibrosis (i.e., F0 and F1).

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 direct-acting antiviral drug against the hepatitis C virus (HCV) to act on a target other than the protease. LDV is a new agent 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 eight 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 eight 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.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of LDV/SOF, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with CHC infection.

Patient Input Information
The following is a summary of information provided by six 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 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, interferon-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 coinfection, were excluded in all trials.

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, 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, 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 SVR12.

Efficacy

- All treatment groups were statistically significantly superior to the historical control rates for SVR12 ($P < 0.001$). The proportion of patients with SVR12 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 (eight weeks), 93.1% for LDV/SOF+RBV (eight 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 eight 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 (eight weeks), 4.2% for LDV/SOF+RBV (eight 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 (eight weeks), 76.4% for LDV/SOF+RBV (eight 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 (eight weeks), 0.5% for LDV/SOF+RBV (eight 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: No patients in any treatment group
- ION-3: 0% for LDV/SOF (eight weeks), 0.9% for LDV/SOF+RBV (eight 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 eight 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] then 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.

Other Discussion Points:

CDEC noted the following:

- Therapy involving PR is associated with substantial adverse events.
- Patients coinfected with 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 SVR12 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 levels of fibrosis staging.

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 treatment regimens for CHC.
- The pharmacoeconomic consequences of reinfection following treatment with LDV/SOF or other treatment regimens for CHC require further evaluation.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

February 18, 2015 Meeting
Regrets:

Two CDEC members were unable to attend 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*.

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