CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

ASUNAPREVIR
(Sunvepra — Bristol-Myers Squibb)
Indication: Chronic Hepatitis C Genotype 1 and 4 in Adults

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that asunaprevir (ASV) be reimbursed for use in combination with daclatasvir (DCV) in genotype 1b chronic hepatitis C (CHC) infection, and in combination with DCV and pegylated interferon plus ribavirin (PR) in genotype 1 and 4 CHC, provided the following conditions are met:

Conditions:
- The drug plan cost of a treatment course with asunaprevir combination treatment should provide cost savings when compared with the drug plan cost of a course of treatment with the least costly alternative comparable treatment option.
- Treatment managed by a professional with expertise in the treatment of CHC infection.

Reasons for the Recommendation:
1. A review of four open-label clinical trials suggests the clinical response rates observed with the asunaprevir combination regimens used are clinically meaningful and comparable with those observed in other studies for interferon-free treatment regimens in similar CHC populations. Because there are no direct comparisons to currently available interferon-free regimens and no established methods for performing indirect treatment comparisons, there is uncertainty regarding clinical comparable efficacy. There is no clinical evidence that the new treatment is superior to funded alternatives.
2. There is uncertainty regarding the cost-effectiveness of ASV combination regimens compared with currently available therapies for both genotype 1 and genotype 4 CHC infection (particularly compared with interferon-free therapies), given the lack of direct data to determine comparative efficacy and safety.

Of Note:
1. CDEC noted there would be limited use of PR-based regimens, given the number of interferon-free regimens available for the treatment of CHC infection.
2. CDEC noted there was a reduced response rate in patients infected with hepatitis C virus (HCV) with an L31 or Y93 HCV NS5A-resistant variant at baseline. Given the prevalence rate of resistance observed in the Hallmark DUAL trial and the subsequent reduced response rate in these patients, further research is needed to ascertain the relevance and

utility of resistance testing in determining the appropriate treatment regimen to individualize patient treatment with CHC regimens.

Other Discussion Points:

- No direct evidence was available on the comparative efficacy and safety of ASV combined with DCV or DCV + PR versus other direct-acting antiviral (DAA) regimens or combinations currently in use in Canada. According to the *CADTH Therapeutic Review for Drugs for Chronic Hepatitis C Infection*, the rate of sustained virologic response 12 weeks after the end of treatment (SVR12) was statistically significantly lower for DCV + ASV compared with ledipasvir/sofosbuvir and was not statistically significantly different from sofosbuvir/ribavirin or ombitasvir/paritaprevir/ritonavir + dasabuvir in treatment-naive genotype 1b CHC patients. In treatment-experienced genotype 1b patients, SVR12 was statistically significantly lower for DCV + ASV than ombitasvir/paritaprevir/ritonavir + dasabuvir and not significantly different compared with ledipasvir/sofosbuvir. Among treatment-experienced genotype 1 CHC patients, no statistically significant differences in SVR12 were detected between DCV/ASV + PR and other interferon-free DAA regimens. These estimates were based largely on data from single-arm trials, and thus are associated with greater uncertainty than indirect treatment comparisons based on controlled trials. Therefore, they must be interpreted in the context of the uncertainty associated with methods for synthesizing evidence from single-arm trials.
- Efficacy of these drugs in patients with decompensated liver disease, hepatitis B or HIV coinfection, malignancy, or recent substance abuse is uncertain. However, these patients are often in greatest need of treatment, and experience with other drugs indicates that it is likely that DCV + ASV will also be effective and safe for these patients.

Background:

Asunaprevir, a DAA agent against HCV, is a highly selective inhibitor of the HCV nonstructural protein 3/4A (NS3/4A) replication complex. Asunaprevir has a Health Canada indication for use in combination with other agents for the treatment of CHC infection in adults with HCV genotype 1 or 4 infection and compensated liver disease (including cirrhosis).

Asunaprevir is available as a 100 mg capsule. The recommended dose is 100 mg, taken orally, twice daily for 24 weeks for adults who are treatment-naive or treatment-experienced, with or without compensated cirrhosis, in combination with:

- DCV for genotype 1b patients; or
- DCV + PR for genotype 1 and 4 patients.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of ASV and a critique of the manufacturer's pharmacoeconomic evaluation and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

Four patient groups — the Canadian Liver Foundation (CLF), Canadian Treatment Action Council (CTAC), the Pacific Hepatitis C Network, and the Hepatitis C Education and Prevention Society — responded to the CDR call for patient input. Information for the patient input submissions was obtained through interviews with patients affected by hepatitis C, caregivers of

patients, physicians who treated patients with ASV, and online surveys. The following is a summary of information provided by the patient groups:

- 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 ASV are that it will address unmet patient needs.

Clinical Trials

The systematic review included four open-label clinical trials, including one RCT (Study 031) and two uncontrolled trials (Hallmark DUAL and NIPPON) of DCV + ASV in patients with genotype 1b CHC, and one uncontrolled study (Hallmark QUAD) of DCV/ASV + PR in patients with genotype 1 and 4 CHC. The trials included treatment-naive (DUAL, 031), treatment-experienced (DUAL, NIPPON), and interferon-ineligible or -intolerant cohorts (DUAL, NIPPON); sample sizes per treatment cohort ranged from 44 to 235 patients. Study 031 assessed whether DCV + ASV was non-inferior to telaprevir (TEL) plus PR: all other trials did not have a control group.

Outcomes

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

- SVR12 or 24 — defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) 12 or 24 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 undetectable HCV RNA at the end of treatment.
- Short Form (36) Health Survey (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. The SF-36 consists of eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health) with scores ranging from 0 (worst) to 100 (best).

The primary outcome in all studies was the proportion of patients who achieved SVR12 or SVR24.

Efficacy

- Among patients who received DCV + ASV for 24 weeks, the proportion of patients with SVR12 or 24 was reported as follows:
    - DUAL: genotype 1b treatment-naive 90%
    - DUAL: genotype 1b treatment-experienced 82%
    - DUAL: genotype 1b ineligible or intolerant to interferon 82%
    - NIPPON: genotype 1b treatment-experienced 81%
    - NIPPON: genotype 1b ineligible or intolerant to interferon 88%.

- In Study 031, DCV + ASV was deemed non-inferior to TEL + PR in terms of SVR12. The proportion of treatment-naive genotype 1b CHC patients with SVR 12 was reported as follows:
    - DCV + ASV 89%
    - TEL + PR 66%.
- Among patients who received DCV/ASV + PR for 24 weeks, the proportion of patients with SVR12 was reported as follows:
    - QUAD: genotype 1 treatment-experienced 93%
    - QUAD: genotype 4 treatment-experienced 98%.
- Relapse was reported in 3% of treatment-naive and 4% to 9% of treatment-experienced or interferon-ineligible or -intolerant genotype 1b patients in the DUAL and NIPPON trials. In Study 031, 8% of patients who received DCV + ASV relapsed compared with 19% who received TEL. In the QUAD study, 2% of genotype 1 and no genotype 4 patients reported a relapse.
- 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 + ASV for 24 weeks.

Harms (Safety and Tolerability)

The most commonly reported adverse events for DCV + ASV regimens included headache (13% to 31%), nausea (4% to 17%), and fatigue (2% to 42%). The proportion of patients who experienced at least one adverse event was reported as follows:

- DUAL: 81% to 87%
- NIPPON: 85% to 87%
- QUAD: 99%.

- The proportion of patients who experienced at least one serious adverse event was reported as follows:
    - DUAL: 5% to 7%
    - NIPPON: 5% to 7%
    - QUAD: 6%.
- The proportion of patients who experienced an adverse event leading to discontinuation of any study drug was reported as follows:
    - DUAL: 1% to 3%
    - NIPPON: 2% to 7%
    - QUAD: 5%.
- In Study 031, the proportion of patients who reported adverse events in the DCV + ASV versus TEL + PR groups, respectively, was as follows:
    - Any adverse event: 89% versus 100%
    - Serious adverse events: 4% versus 5%
    - Discontinued treatment due to adverse events: 5% versus 20%.

Cost and Cost-Effectiveness

ASV is available as 100 mg capsules at a confidential price of or $[redacted] per capsule, or $[redacted] for 24 weeks. The recommended dose is 100 mg twice daily for 24 weeks. For patients with genotype 1b, ASV is to be used in combination with DCV 60 mg daily for 24 weeks (total cost of treatment course: $[redacted]). For patients with genotype 1 or 4, ASV is to be used in combination with DCV and PR for 24 weeks (total cost of treatment course: $[redacted]). For all analyses, the manufacturer assumed that the price of a 24-week course of DCV will be capped at [redacted]; i.e., total cost of DCV will not exceed $[redacted].

The manufacturer submitted a cost-utility analysis over a lifetime horizon (up to 100 years of age) from a Ministry of Health perspective. The pharmacoeconomic model submitted included both a DCV plus sofosbuvir (SOF) regimen, as well as the ASV-containing regimens above. The analysis assessed the cost-effectiveness of two ASV-containing regimens across treatment-naive and/or treatment-experienced subgroups with various genotypes of HCV (genotype 1, 1b, 4). The comparators varied by genotype and consisted of DAAs in combination with PR, including SOF, simeprevir (SIM), TEL, and boceprevir (BOC), SOF plus ribavirin (RBV) and PR alone. The submission used the MOdelling the NAtural histoRy of Cost-effectiveness of Hepatitis (MONARCH) model, which tracks patients through Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis states through to decompensated cirrhosis, complications (hepatocellular carcinoma, liver transplantation), and death. Where SVR is obtained, patients move to a set of SVR-specific states in which relapse to HCV-positive states does not occur and progression is limited only to the case where SVR was obtained following existing compensated cirrhosis. The manufacturer reported that ASV-containing regimens led to an incremental cost-utility ratio (ICUR) below $50,000 per quality-adjusted life-year (QALY) in treatment-naive and treatment-experienced patients with HCV genotype 1b, partial responders with HCV genotype 1, and a mixed treatment-experienced group (partial and null responders) with HCV genotype 4.

CDR noted that caution should be exercised in concluding that ASV-containing regimens are cost-effective, as the model did not include relevant comparators — specifically, no-treatment and other interferon-free regimens. Clinical data to allow comparisons across all subgroups (treatment-naive, partial responders, null responders, relapsers) were not available for all genotypes. Efficacy and adverse event data (including discontinuation) were obtained through matching-adjusted indirect comparisons (MAICs) and naive indirect treatment comparisons. Across the MAIC cases (and especially for genotype 1b), the resulting data lacked credibility, as figures for the same ASV-containing regimens, in the same patients, differ by an order of magnitude simply because the comparator is different. Other limitations included the lack of relapse and/or reinfection states, as this will overstate the cost-effectiveness of curative treatments. The manufacturer's models contained errors, and in particular there were issues with mortality in patients with advanced disease. This issue was corrected by CDR reviewers for this report, as well as an additional issue regarding the characterization of uncertainty.

Even when ASV-containing regimens appear to be cost-effective based on CDR reanalyses, they have not been compared against newer alternatives and the presented evidence also often considers only a limited range of existing therapies. Based on the available economic model and data, CDR reanalyses suggest the following:

- For treatment-naive patients, by genotype
    - Genotype 1b: there is some evidence that DCV + ASV is cost-effective against PR, but some caution should be placed on this finding as SOF + PR, SIM + PR, and interferon-free regimens were not included.
    - Genotype 1 and 4: the DCV/ASV + PR regimen was not included in the model, so no conclusion can be made for this regimen in these populations.
- For treatment-experienced patients, by genotype
    - Genotype 1: for partial responders, quad therapy (DCV/ASV + PR) is cost-effective compared with PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.
    - Genotype 1b: for a number of subgroups (partial responders, null responders, relapsers), DCV + ASV is cost-effective versus PR and dominates BOC + PR, although SOF + PR, SIM + PR, and interferon-free regimens were not included.

- Genotype 4: for null responders, quad therapy (DCV/ASV + PR) appears cost-effective against PR, with SOF + RBV dominated (note that none of the CDR-participating drug plans currently reimburse SOF for G4). However, there is a concern that data for quad therapy were based on treatment-experienced patients, while for comparator treatments, data were obtained from a treatment-naive group.

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.

June 15, 2016 Meeting

Regrets:

One CDEC member did not attend

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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