CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**GLECAPREVIR / PIBRENTASVIR (MAVIRET — ABBVIE CORPORATION)**
Indication: Chronic hepatitis C virus infection

**RECOMMENDATION:**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that glecaprevir/pibrentasvir be reimbursed for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis, including patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors, if the following conditions are met:

**Conditions:**
- The patient is under the care of a physician with experience in the diagnosis and management of HCV infection.
- Drug plan cost for glecaprevir/pibrentasvir should not exceed the drug plan cost of treatment with the least costly direct-acting antiviral agent(s) (DAA).


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# GLECAPREVIR/PIBRENTASVIR (MAVIRET — ABBVIE CORPORATION)

Indication: Chronic hepatitis C virus (HCV) infection.

## Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that glecaprevir/pibrentasvir (GP) be reimbursed for the treatment of adult patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis, including patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not with both classes of inhibitors, if the following conditions are met:

## Conditions:

- The patient is under the care of a physician with experience in the diagnosis and management of HCV infection.
- The drug plan cost for GP does not exceed the drug plan cost of treatment with the least costly direct-acting antiviral (DAA) agent(s).

## Reasons for the Recommendation:

1. Evidence from 10 studies indicated that treatment with GP for 8, 12, or 16 weeks was associated with a high percentage of patients achieving a sustained virologic response at 12 weeks (SVR12). The percentage of patients who achieved SVR12 ranged from 90.9% to 99.7% in adults with HCV genotype 1 to 6 infection who were treatment-naive, had previously received interferon- or sofosbuvir/ribavirin-based treatment, or who had end-stage renal disease. The percentage of DAA-treatment-experienced genotype 1 patients who achieved SVR12 was 88.6%, and 91.5% among those who received GP for 12 or 16 weeks.
2. Only two of the reviewed studies included comparisons with other DAA-based treatments (sofosbuvir/daclatasvir and sofosbuvir/ribavirin); however, important limitations prevent drawing conclusions about the comparative benefit and harms with GP from these two studies. There were no studies comparing GP with other pan-genotypic DAA regimens available in Canada, such as sofosbuvir/velpatasvir (Epclusa) or sofosbuvir/ledipasvir (Harvoni).
3. There is insufficient evidence that GP is clinically superior to the least costly alternative DAA treatment for patients with HCV infection.

## Of Note:

In making decisions regarding treatment eligibility, jurisdictions may consider the cost impact on drug plans and overall health care system sustainability. The drug plan cost of treatment with GP should not exceed the drug plan cost of treatment with the least costly DAA alternative.

## Discussion Points:

- CDEC noted that the eight-week treatment duration of GP among treatment-naive HCV patients without cirrhosis (which is likely the largest proportion of HCV patients) is shorter than the course of treatment for other available DAAs.
- GP is one of only two drugs approved by Health Canada for treating patients with prior DAA treatment experience, although CDEC noted that GP has a narrower indication in this population of patients than the other Health Canada–approved product, sofosbuvir/velpatasvir/voxilaprevir (Vosevi).
- The product monograph for GP indicates that it has the potential for many drug–drug interactions, which may limit its use in patients with certain comorbidities and those coinfected with HCV and HIV.

- GP is one of only a few DAA-based products approved by Health Canada for use in patients with end-stage renal disease (ESRD), including patients on dialysis. CDEC noted that of these treatment options, GP is the only pan-genotypic regimen.
- All of the trials reviewed for GP excluded patients with hepatitis B virus coinfection; thus, the trials did not provide any data with respect to the risk of hepatitis B virus reactivation. The Committee noted that the product monograph for GP contains a warning regarding the potential risk for hepatitis B virus reactivation, as do the product monographs for many other DAAs approved by Health Canada.

## Background:

GP has a Health Canada indication for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor, but not with both classes of inhibitors. These pan-genotypic DAAs belong to the NS3/4A protease inhibitor drug class (glecaprevir) and the NS5A inhibitor drug class (pibrentasvir). The product is available as a fixed-dose combination tablet containing 100 mg of glecaprevir and 40 mg of pibrentasvir, and the Health Canada–approved dose is three tablets (i.e., 300 mg/120 mg) once daily for 8, 12, or 16 weeks, depending on the patient's prior treatment experience, genotype, and presence of cirrhosis.

## Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of pivotal and randomized controlled trials of GP and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience treating patients with HCV, and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by HCV.

### Patient Input Information

Patient input was received from the Canadian Liver Foundation, Canadian Treatment Action Council, the Pacific Hepatitis C Network, and the Hepatitis C Education and Prevention Society. The information was gathered through interviews with patients and caregivers affected by hepatitis C as well as with health care professionals, and through surveys, social media, meetings with support groups, informal discussions, and via a webinar that included patients diagnosed with hepatitis C. Information gathered from previous patient input consultations from other hepatitis C drugs was used as well. The following is a summary of key input from the perspective of the patient groups:

- Patients experience a variety of physical symptoms, as well as anxiety, depression, stigma, and isolation as a result of HCV infection. They and their families also often bear serious financial hardships.
- Patients expect high cure rates with GP across all genotypes, even among those who are more difficult to treat or who have complicated health conditions.
- Many patients stress the value of the shorter treatment duration, which may be only eight weeks for some patients, and fewer adverse effects with GP than with previous interferon (IFN)-based treatments.

### Clinical Trials

The systematic review included data from 10 unique studies in patients with HCV genotype 1 to 6 infection. Three trials were open-label single-arm studies (EXPEDITION-1, EXPEDITION-4, ENDURANCE-4) and four trials were open-label studies that randomized or assigned patients to more than one GP treatment group (ENDURANCE-1, SURVEYOR-II Part 3 and Part 4, MAGELLAN-1 Part 2). Two trials were open-label randomized controlled noninferiority trials (CERTAIN-2, ENDURANCE-3) and one trial was a randomized double-blind study (ENDURANCE-2).

The GP treatment duration was 8, 12, or 16 weeks among the included studies. Three trials (ENDURANCE-1, ENDURANCE-2, SURVEYOR-II Part 4) compared the percentage of patients who achieved SVR 12 after the end of treatment with GP versus a historical control to determine noninferiority. Two controlled trials were designed to assess the noninferiority of GP treatment for 8 weeks versus sofosbuvir/ribavirin (SOF/RBV) treatment for 12 weeks (CERTAIN-2), or GP treatment for 12 weeks versus SOF/daclatasvir (DCV) treatment for 12 weeks (ENDURANCE-3). The double-blind randomized controlled trial ENDURANCE-2 was designed to assess safety of GP treatment for 12 weeks versus placebo.

Patients with all genotypes were enrolled, including those who were treatment-naive (nine trials), had prior IFN-based or SOF/RBV-based treatment experience (eight trials), prior DAA treatment experience (one trial), ESRD (one trial) or HIV coinfection (one trial). Patients with cirrhosis were included in three trials and those without cirrhosis were included in nine trials. In total, 2,180 patients received GP. Across the trials, 0% to 2.6% of patients per treatment group withdrew from the studies.

The key limitation was the lack of comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group. All but one of the studies was open-label.

## Outcomes

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

- SVR12 was defined as HCV RNA below the lower limit of quantitation (LLOQ) 12 weeks after the last actual dose of the study drug.
- Relapse was defined as confirmed HCV RNA ≥ LLOQ between the end of treatment and 12 weeks after the last dose of the study drug among patients who completed treatment as planned, with HCV RNA below LLOQ at the end of treatment.
- On-treatment virologic failure was defined as a confirmed increase during treatment of more than 1 $\log_{10}$ IU/mL above nadir in HCV RNA, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA had been below LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least six weeks 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 (HRQoL). 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.
- EuroQol 5-Dimensions (EQ-5D) questionnaire — a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments. The descriptive portion of the EQ-5D consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. The second part of the EQ-5D is a 20-cm visual analogue scale that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.”
- Harms outcomes.

The primary outcome in all trials was SVR12.

## Efficacy

- Among studies that enrolled non-cirrhotic patients, 90.9% to 99.7% of patients achieved SVR12 and the response rates were similar among those who received GP for 8 weeks (93.1% to 99.1%) or 12 weeks (90.9% to 99.7%). These studies included patients with all genotypes who were either treatment-naive or had prior IFN- or SOF/RBV-based treatment.
- GP for 12 weeks was noninferior to SOF/DCV in treatment-naive, non-cirrhotic patients with HCV genotype 3 infection, although the relevance of this finding is unclear given that 8 weeks is the approved duration for GP in this population. GP treatment for 8 weeks was also noninferior to SOF/RBV for 12 weeks in non-cirrhotic treatment-naive and prior IFN-based treatment-experienced Japanese patients with HCV genotype 2 infection. In non-cirrhotic HCV genotype 1 patients (treatment-naive or prior IFN-based therapy), GP for 8 weeks was noninferior to GP for 12 weeks.

- Two trials enrolled only patients with compensated cirrhosis and showed an SVR12 rate ranging from 95.7% to 99.3% among treatment-naive and IFN- or SOF/RBV-based treatment-experienced patients with HCV genotype 1, 2, 4, 5, or 6 infection.
- The SVR12 rate was 98.1% among the cirrhotic and non-cirrhotic patients with ESRD.
- Among genotype 1 patients with prior DAA treatment experience, the SVR12 rate was 88.6% in patients who received GP for 12 weeks and 91.5% in those who received 16 weeks of treatment. Subgroup data by treatment history showed all NS3/4A inhibitor–experienced patients achieved SVR12 (100%, total N = 27), and 88% and 94% of NS5A-experienced patients (total N = 34), achieved SVR 12.
- Few patients experienced an on-treatment virologic failure or relapse (0 to 2 patients per group; < 1.5%) except for the study of patients with prior DAA treatment failure (MAGELLAN-1 Part 2; 8.5% to 11.4% per group) or in genotype 3 patients in the ENDURANCE-3 (1.7% to 3.8%) or SURVEYOR-II studies (0% to 9.1%).
- No statistically significant differences in HRQoL were detected between GP and placebo, SOF/DCV or SOF/RBV in HRQoL based on the SF-36 or EQ-5D in three trials. Outcomes reported by patients in these and the other trials were difficult to interpret due to limitations in the data, including the open-label design, missing data, analysis methods used (i.e., no imputation of missing data or control of multiplicity), or the lack of a control group.

## Harms (Safety and Tolerability)

- The majority of patients in all trials experienced one or more adverse events with headache, fatigue, and nausea reported most frequently among those who received GP. In the double-blind placebo-controlled trial, 65% and 58% of patients reported adverse events in the GP and placebo groups, respectively.
- The frequency of serious adverse events was highest (24%) in patients with ESRD and those in EXPEDITION-1 (7.5%), which only enrolled patients with compensated cirrhosis. In other trials, the frequency of serious adverse events among GP-treated patients ranged from 0.8% to 4.6% and was similar for GP and placebo or SOF/DCV.
- None of the trials were designed to assess longer-term safety, or hepatic-related morbidity or mortality, which are important to patients.

## Cost and Cost-Effectiveness

At the time of submission, the manufacturer submitted a price of $797.62 per day (three tablets). This price was reduced by the manufacturer during the review to $714.29 per day (three tablets), reflecting an approximate 10% reduction in the original price, and corresponding to $40,000 for an eight-week (56-day) treatment, $60,000 for a 12-week (84-day) treatment and $80,000 for a 16-week (112-day) treatment.

The manufacturer submitted a cost-utility analysis comparing GP with a number of approved and funded interferon-free regimens: sofosbuvir/velpatasvir (SOF/VEL), sofosbuvir/ledipasvir (SOF/LDV), grazoprevir/elbasvir (GZR/EBR), ombitasvir/paritaprevir/ritonavir/dasabuvir (OBV/PTV/r/DSV), and SOF/RBV. The effectiveness parameters used in the model were drawn from non-comparative trials; there was no formal indirect comparison of trials of relevant comparators but there were naive comparisons drawing on SVR results from individual trial arms. The manufacturer used a Markov cohort model where patients are located in one of 13 mutually exclusive health states, with the model structure allowing patients to enter the model either as non-cirrhotic (F0–F3) or with compensated cirrhosis (F4). A lifetime horizon was used and the analysis was conducted from the perspective of the Canadian publicly funded health care system. The manufacturer included two approaches for the base-case analysis: a portfolio approach that reflects a pan-genotypic HCV patient population, and a segmented approach where individual patient groups were considered, with a primary focus on genotype 1−infected, non-cirrhotic, treatment-naive patients.

The manufacturer reported in the portfolio approach that GP dominates comparators (GP is associated with higher quality-adjusted life-years [QALYs] and lower costs). In the segmented approach, GP appeared to be cost-effective for treatment-naive patients

without cirrhosis in all subgroups when compared with no treatment. For treatment-naive patients with cirrhosis, when compared with SOF/VEL, GP ranged from being dominated by SOF/VEL (genotypes 2, 4, 5, and 6) to dominating SOF/VEL in genotypes 1 and 3.

In patients experienced with pegylated interferon/ribavirin plus sofosbuvir treatment, GP compared with SOF/VEL ranged from being dominated (for patients with cirrhosis) to being dominant (for patients without cirrhosis) for genotype 1; while for genotype 3, the incremental cost-utility ratio for GP was $99,877 per QALY (patients without cirrhosis) and $69,314 per QALY (patients with cirrhosis) compared with SOF/VEL. In genotype 1 patients experienced with NS5A or NS3/4A treatment, the incremental cost-utility ratios for GP compared with no treatment were $13,097 per QALY and $6,383 per QALY, respectively.

CDR identified the following key limitations with the manufacturer's economic submission:

- The portfolio approach submitted by the manufacturer was considered invalid based on the approved indications for GP in genotypes based on treatment experience and the presence or absence of cirrhosis. As such, the focus was on the segmented analyses.
- There was uncertainty with the clinical evidence for GP in two respects:
  - The effectiveness parameters were drawn from non-comparative trials.
  - The sample size of many subgroups with reported 100% SVR rates was small and uncertainty in these estimates was not accounted for appropriately.
- The efficacy parameters in genotype 1 patients previously treated with NS3/4A protease inhibitors or NS5A inhibitors were based on a clinical trial that was not designed or powered to test for subgroup effects. The efficacy for GZR/EBR in the same analysis was based on a study that used an unapproved dosage for GZR/EBR.

CDR attempted to address whatever limitations it could, with the results indicating that GP is more cost-effective in genotypes 1 and 2 in treatment-naive or -experienced patients without cirrhosis than in patients with cirrhosis due to the lengthier treatment duration in cirrhotic versus non-cirrhotic patients (12 weeks versus 8 weeks), which leads to increased total costs associated with GP therapy. A price reduction of up to 12% may be required for GP to be cost-effective in genotype 3 patients. However, as clinical uncertainty could not be addressed in CDR reanalyses, given the lack of comparative information for subgroups of interest, the cost-effectiveness results of GP and suggested price reductions warrant cautious consideration when interpreted. No conclusions could be drawn regarding the cost-effectiveness of GP for patients with genotype 4, 5, or 6 due to the limited data included in the submitted model.

## CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

## December 13, 2017 Meeting

## Regrets:

Two CDEC members did not attend.

## Conflicts of Interest:

None.