CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

ELBASVIR/GRAZOPREVIR
(Zepatier — Merck Canada Inc.)
Indication: Chronic Hepatitis C Genotypes 1, 3, or 4 Infection in Adults

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that elbasvir/grazoprevir (EBR/GZR) be reimbursed for the treatment of chronic hepatitis C virus (CHC) genotypes 1, 3, and 4 infections in adults, if the following conditions are met:

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. Based on data from seven trials (two randomized, double-blinded placebo-controlled trials that also compared EBR/GZR versus a historical control [C-EDGE Treatment-Naive, and C-SURFER], two trials that compared EBR/GZR versus a historical control [C-EDGE Treatment-Experienced, and C-EDGE Coinfection], and three uncontrolled, open-label trials [C-WORTHY, C-SALVAGE, and C-SCAPE]), EBR/GZR demonstrated high rates of sustained virologic response at 12 weeks (SVR12) in in both treatment-naive and treatment-experienced patients with genotype 1 or 4 CHC infection; in addition, a high SVR12 rate was reported in treatment-naive patients with genotype 1 or 4 CHC infection who were coinfected with HIV. Furthermore, EBR/GZR was associated with high rates of SVR12 in treatment-naive and treatment-experienced patients with genotype 1 CHC infection with chronic kidney disease (CKD).
2. One open-label, phase 2 pivotal trial (C-SWIFT) demonstrated that treatment with EBR/GZR in combination with sofosbuvir (SOF) was associated with high rates of SVR12 in patients with genotype 3 CHC infection who were treatment-naive without cirrhosis (100.0%; 95% confidence interval [CI], 76.8% to 100%) or treatment-naive with cirrhosis (83.3%; 95% CI, 51.6% to 97.9%).
3. EBR/GZR is cost-effective for patients with genotype 1 or 4 CHC infection regardless of cirrhosis status and prior treatment experience. In genotype 3, EBR/GZR is not considered to be cost-effective at the submitted price.
4. Jurisdictions may consider the cost impact to drug plans and overall health care system sustainability in making decisions regarding treatment eligibility.

Of Note:

1. CDEC noted that some patients will be infected with nonstructural protein 5A (NS5A) resistance-associated variants (RAVs), which may result in decreased drug efficacy or require a longer period of treatment. The clinical expert noted that the issue of resistance is not unique to the EBR/GZR regimen and that the use of resistance testing to guide patient management is an evolving area; the accessibility and cost impacts of such testing remain to be determined.
2. 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, first-served basis, priority for treatment should be given to patients with more severe disease.
3. EBR/GZR has been found to be safe and effective in patients with CKD.
4. Drug plan costs for EBR/GZR should not exceed the drug plan costs of other interferon-free regimens for the treatment of CHC.

Research Gaps:

The Committee proposed that the following issues be addressed through research as a high priority in future to facilitate comparisons of interferon-free direct-acting antiviral agent (DAA) therapies for CHC:

- There are no data that directly or indirectly compare EBR/GZR against other interferon-free DAA regimens for CHC.
- Further research is needed to determine the relevance and utility of resistance testing in determining appropriate treatment regimen selection and duration to individualize patient treatment for all CHC regimens.

Background:

This product is a fixed dose combination of EBR and GZR, which are DAAs against the hepatitis C virus (HCV). EBR is an HCV NS5A inhibitor and GZR is an HCV NS3/4A protease inhibitor. Zepatier has a Health Canada indication for use alone or in combination with other drugs for the treatment of CHC genotypes 1, 3, or 4 infection in adults. Zepatier is formulated in one tablet; the tablet is composed of 100 mg GZR and 50 mg EBR. The recommended dose is one tablet daily alone or in combination with SOF or ribavirin (RBV), as follows:

- Genotype 1 or 4 treatment-naive (TN) and peginterferon alfa plus ribavirin (PR) treatment-experienced (TE) relapsers: 12 weeks of treatment with EBR/GZR
- Genotype 1 protease inhibitor (PI)/PR-TE relapsers: 12 weeks of treatment with EBR/GZR
- Genotype 1b TN; non-cirrhotic patients: eight weeks of treatment with EBR/GZR
- Genotype 1b PR- or PI/PR-TE on-treatment virologic failures: 12 weeks of treatment with EBR/GZR
- Genotype 1a PR- or PI/PR-TE on-treatment virologic failures: 16 weeks of treatment with EBR/GZR plus RBV
- Genotype 4 PR-TE on-treatment virologic failures: 16 weeks of treatment with EBR/GZR plus RBV
- Genotype 3 TN patients: 12 weeks of treatment with EBR/GZR plus SOF.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of EBR/GZR, 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 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 even 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, discrimination, or ostracism.
- Spouses and loved ones who care for patients with CHC infection are faced with a substantial burden, as the symptoms of the infection 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 EBR/GZR are to address the gaps in treatment and the unmet needs of HCV patients, such as those who had a null response or relapsed, those who have contraindications or cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes. Patients also have high expectations of a cure with EBR/GZR. Once cured, they expect that their fibrosis or cirrhosis will reverse and their risk of end-stage liver disease will be reduced.
- Patients emphasize that they are looking to receive treatment as early as possible, regardless of their disease status. The accessibility and affordability with EBR/GZR are of great concern to HCV patients.
- Patients see advantages with EBR/GZR that include shorter duration of treatment, fewer adverse effects, smaller pill burden and, most important to patients, high response rates.

Clinical Trials
The CDR systematic review included eight trials. Two trials were randomized, double-blinded placebo-controlled trials (C-EDGE Treatment-Naive [N = 421], and C-SURFER [N = 237]); three trials were randomized, parallel-group, open-label trials (C-EDGE Treatment-Experienced [N = 420], C-SWIFT [N = 143], and C-WORTHY [N = 573]), and three were open-label, non-randomized trials (C-EDGE Coinfection [N = 218], C-SALVAGE [N = 79], and C-SCAPE [N = 98]). The trials evaluated 12-week treatment with EBR/GZR alone (C-EDGE Treatment-Naive, C-SURFER, C-EDGE Coinfection, and C-SCAPE), eight-week or 12-week treatment with EBR/GZR alone (C-WORTHY), 12-week treatment with EBR/GZR plus RBV (C-SALVAGE), 12-week treatment with EBR/GZR or 16-week treatment with EBR/GZR plus RBV (C-EDGE Treatment-Experienced), or 12-week treatment with EBR/GZR plus SOF (C-SWIFT). The trials enrolled adults with CHC genotype 1, 4, or 6 (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced), genotype 1 (C-SURFER, C-SALVAGE), genotype 1 or 3 (C-SWIFT, C-WORTHY), or genotypes 2, 4, 5 or 6 (C-SCAPE). Four trials enrolled patients who were TN (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SWIFT, C-SCAPE); two trials included TE patients (C-EDGE Treatment-Experienced, C-SALVAGE), and two trials included

TN and TE patients (C-SURFER, C-WORTHY). In the C-EDGE Treatment-Experienced study, the patients had a prior null, partial response or relapse to PR, while the TE patients in the C-SALVAGE study had prior non-response, breakthrough, or relapse to PR + DAA. In the C-SURFER study, the TE patients had prior interferon or PR treatment failures, and were null responders, partial responders, or relapsers. Patients included in C-EDGE Coinfection study were coinfected with HIV, and patients included in C-SURFER study had CKD. All trials excluded patients with decompensated liver disease, hepatitis B coinfection, malignancy, prior organ transplant (except the C-SURFER trial, which included patients with prior kidney transplant), or recent substance abuse. The C-EDGE Treatment-Naive, C-SURFER, C-SWIFT, C-SALVAGE, and C-SCAPE trials excluded patients coinfected with HIV. Only the C-SCAPE trial excluded patients with cirrhosis; the rest of the trials included both cirrhotic and non-cirrhotic patients.

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.
- 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 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. 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 HRQoL 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).
- EuroQol Visual Analogue Scale (EQ VAS) — a 20 cm visual analog scale that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.”
- Work Productivity and Activity Impairment (WPAI) 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

- In the C-EDGE Treatment-Naive study, the SVR12 rate was 95% (95% CI, 92% to 97%) in the TN genotypes 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks. The lower bound of the 95% CI (92%) exceeded the 73% historical control rate.
- In the C-EDGE Coinfection study, the SVR12 rate was 95% (95% CI, 91% to 98%) in the TN genotypes 1, 4, or 6 CHC patients who are coinfected with HIV and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (91%) exceeded the 70% historical control rate.

- In the C-SURFER study, the SVR12 rate was 94% (95% CI, 89% to 98%) in the TN or TE genotype 1 CHC patients who have CKD and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (95%) exceeded the 45% reference SVR rate.
- In the C-EDGE Treatment-Experienced study, the SVR12 rates were 92%; 95% CI (86% to 97%), and 97% (95% CI, 92% to 99%) in the TE genotype 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks and EBR/GZR + RBV for 16 weeks, respectively. The lower bound of each 95% CI (86% and 92%) exceeded the 58% historical control rate.
- Overall, EBR/GZR for 12 weeks achieved SVR12 rates between 90% and 100% among patients with genotype 1 CHC and showed similar response rates regardless of the patients' prior treatment history, genotype subtype, presence of CKD, or presence of cirrhosis.
- EBR/GZR for 12 weeks also achieved SVR12 rates between 87% and 96% among TN patients with genotype 1 CHC who were coinfected with HIV (C-EDGE Coinfection, and C-WORTHY trials).
- EBR/GZR for eight weeks achieved SVR12 rates of 97% among TN patients with genotype 1b CHC with METAVIR fibrosis score of F0 to F2 (C-WORTHY trial).
- Among PR-TE patients who received EBR/GZR + RBV for 16 weeks, an SVR rate of 95% was reported for genotype 1a, while those with genotype 1b achieved an SVR rate of 100% (C-EDGE Treatment-Experienced trial).
- Patients with prior treatment experience with DAA who received EBR/GZR + RBV for 12 weeks had a response rate of 96% in patients with genotype 1a and 98% in patients with genotype 1b (C-SALVAGE trial).
- TN patients with genotype 4 who received EBR/GZR for 12 weeks, SVR12 ranged from 90% to 100% (9/10 [90%] in the C-SCAPE trial, 18/18 [100%] in the C-EDGE Treatment-Naive trial, and 27/28 [96.4%] in C-EDGE Coinfection trial), while the SVR rate was 78% (7/9 [77.8%] in the C-EDGE Treatment-Experienced trial).
- TE patients with genotype 4 who received EBR/GZR + RBV for 16 weeks achieved an SVR rate of 100% (8/8 [100%] in the C-EDGE Treatment-Experienced trial).
- Only the C-SWIFT trial included patients with genotype 3. For TN non-cirrhotic patients with genotype 3 who received EBR/GZR + SOF for 12 weeks, the response rate was 100%, while cirrhotic patients had a response rate of 83%.
- The included trials reported few cases of relapse. The reported relapses were associated with the presence of NS5A polymorphisms. In the C-EDGE Treatment-Naive trial, among the 10 genotype 1a–infected patients who experienced virologic failure, nine (90%) had treatment-emergent NS5A RAVs at failure. In the single genotype 1b–infected patient who experienced virologic failure, a treatment-emergent NS5A RAV was detected at failure. Also in the C-EDGE Coinfection trial, the four relapsed patients were assessed for treatment-emergent mutations and it was found that two patients had NS3 and three had NS5A mutations. In addition, the presence of specific NS5A RAVs in genotype 1a patients is associated with a more than five-fold decrease in EBR in vitro antiviral activity. This may explain the reduced efficacy observed in this subset of patients: 2/9 (22.2%) in the C-EDGE Treatment-Naive trial, 3/4 (75.0%) in the C-EDGE Coinfection trial, and 6/6 (100%) in the C-SURFER trial in TN patients who received EBR/GZR for 12 weeks, and 2/6 (33.3%) in the C-EDGE Treatment-Experienced trial in patients who received EBR/GZR for 12 weeks, and 0/1 (0%) in the C-SALVAGE trial in TE patients who received EBR/GZR +RBV for 12 weeks.
- HRQoL was measured using the SF-36, EQ VAS scores, and CLDQ-HCV in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials. Other patient-reported outcomes (PROs) in these trials included the FACIT-F Scale and the WPAI. HRQoL was also measured using the SF-36 and the EQ VAS scores in the C-SURFER trial.

Across the different PROs, the mean change from baseline in PRO scores during treatment and follow-up did not appreciably differ between EBR/GZR and placebo. The addition of RBV to EBR/GZR did contribute to a worsening of HRQoL, fatigue levels, work productivity, and activity impairment during treatment. Better HRQoL, less fatigue, and less work productivity and activity impairment for EBR/GZR groups were found when compared with the EBR/GZR + RBV groups during the treatment period. At follow-up week 12, HRQoL, fatigue and work productivity and activity impairment scores were similar to or better than the baseline scores in patients treated with EBR/GZR plus RBV.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one adverse event were:
  - 53.3% to 91.7% while on EBR/GZR for 12 weeks
  - 54.8% among those who received EBR/GZR for eight weeks
  - 79.7% among those who received EBR/GZR + RBV for 12 weeks
  - 89.6% among those who received EBR/GZR + RBV for 16 weeks
  - 21.4% to 33.3% among those who received EBR/GZR + SOF for 12 weeks
  - 68.6% to 84.1% among those who received placebo.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - 0% to 3.8% while on EBR/GZR for 12 weeks
  - 0% among those who received EBR/GZR for eight weeks
  - 5.1% among those who received EBR/GZR + RBV for 12 weeks
  - 3.8% among those who received EBR/GZR + RBV for 16 weeks
  - 0% to 14.4% in patients who received EBR/GZR for 12 weeks and have CKD
  - 0% to 8.3% among those who received EBR/GZR + SOF for 12 weeks
  - In those who received placebo, rates were 2.9% in the C-EDGE Treatment-Naive trial and 16.8% for patients with CKD.
- The proportion of patients who experienced an adverse event leading to the discontinuation of any study drug was reported as follows:
  - 0% to 1% while on EBR/GZR for 12 weeks
  - 0% among those who received EBR/GZR for eight weeks
  - 1.3% among those who received EBR/GZR + RBV for 12 weeks
  - 4.7% among those who received EBR/GZR + RBV for 16 weeks
  - 0% among patients who received EBR/GZR for 12 weeks and have CKD
  - 0% among those who received EBR/GZR + SOF for 12 weeks
  - In those patients who received placebo, rates of discontinuation due to adverse events were 1% in the TN group (C-EDGE) and 4.4% in patients with CKD.

Cost and Cost-Effectiveness

At the confidential submitted price ([redacted] per 100/50 tablet), a standard 12-week course of treatment with EBR/GZR would cost [redacted]. For patients requiring 16 weeks of treatment in combination with RBV (e.g., patients with virologic failures with genotype 1a or genotype 4), the cost of treatment is [redacted] to [redacted] (depending on the dose of RBV).

The manufacturer submitted a cost-utility analysis over a lifetime horizon (to 110 years of age) from a provincial Ministry of Health perspective. The cost-effectiveness of EBR/GZR was assessed for TN and TE subgroups, as well as for patients with and without cirrhosis. The comparators varied by genotype and consisted of new DAAs (for genotype 1: ledipasvir + SOF, Holkira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV), simeprevir +

PR, simeprevir + SOF; genotype 1 and 4: SOF + PR; genotype 3: SOF + RBV), PR, and a no-treatment option. The manufacturer used a Markov model that tracks the natural history of the disease, and incorporated the treatment by allowing for SVR states in which disease progression is halted. The manufacturer suggests that EBR/GZR is cost-effective at a $50,000 per quality-adjusted life-year (QALY) threshold in genotype 1 and genotype 4 patients but not cost-effective for TN genotype 3 patients.

The main limitation of the manufacturer's economic submission relates to a lack of justification and detail as to its selected approach in modelling and an unnecessarily complex and opaque model. The lack of transparency complicated the review and assessment of the manufacturer's approach. CDR reanalyses using an alternative model structure and incorporating sensitivity analyses for key input parameters yielded similar results to the manufacturer's analysis. As such, the model is robust to key aspects identified. As a broader issue for consideration, the United States Food and Drug Administration recommends pre-testing for selected genetic mutations for genotype 1 and genotype 4 prior to regimen selection and defining treatment duration in the EBR/GZR monograph. This approach, if taken in Canada, could affect the cost-effectiveness of EBR/GZR.

Overall, the comparative evidence of clinical effectiveness suggests that EBR/GZR is cost-effective for patients with CHC who are genotype 1 and genotype 4, irrespective of cirrhosis status and prior exposure.

In genotype 3, EBR/GZR does not appear to be cost-effective at the submitted price when compared with no treatment or PR; PR appears highly cost-effective versus no treatment. When compared with PR, the incremental cost-utility ratio for EBR/GZR exceeds $60,000 per QALY. Based on CDR reanalyses, a price reduction of 26% to 44% for EBR/GZR would be required, depending on the cirrhosis status of patients.

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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