CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (Genvoya — Gilead Sciences Canada, Inc.) Indication: HIV-1 Infection

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) be listed as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) demonstrated that EVG/COBI/FTC/TAF was non-inferior to EVG/COBI/FTC/tenofovir disoproxil (TDF) for achieving viral load suppression in treatment-naive adults with human immunodeficiency virus (HIV) infection after 48 weeks of treatment. One RCT conducted in virologically suppressed HIV-1 patients demonstrated that switching to EVG/COBI/FTC/TAF from another TDF/FTC-containing regimen was associated with statistically significantly greater rates of virologic suppression at 48 weeks compared with continued therapy with their existing regimen. One open-label, single-group clinical trial demonstrated that treatment with EVG/COBI/FTC/TAF was associated with a virologic success rate of 91.3% for 23 antiretroviral (ARV) treatment-naive adolescents.
2. At the submitted price ([redacted] per tablet), EVG/COBI/FTC/TAF is similar in cost or less costly than other single-tablet or commonly used treatment regimens for adolescents ($41.38 to $43.78) and adults ($41.38 to $55.57) with HIV-1 infection.

Of Note:
CDEC noted that the cost of ARVs may differ across the jurisdictions that participate in the CADTH Common Drug Review (CDR) process.

Background:
EVG/COBI/FTC/TAF has a Health Canada indication for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (weighing 35 kg or more) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF. It is

a single-tablet fixed-dose co-formulation that consists of EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs of EVG/COBI/FTC/TAF, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with HIV-1.

Patient Input Information

One patient group, the Canadian Treatment Action Council, responded to the CDR call for patient input. Information for the submission was collected primarily from a national consultation webinar on the CDR process, on key findings from the EVG/COBI/FTC/TAF clinical trials, and from previous (but recent) consultations. The following is a summary of key information provided by the patient group:

- HIV is a serious, life-threatening disease that compromises a patient's immune system and, if left untreated, predisposes these patients to opportunistic infections.
- In addition to both mental and physical side effects, patients with HIV often experience stress and stigma, and sometimes have difficulty accessing the most effective treatments.
- Patients are increasingly concerned with comorbidities and with side effects associated with particular treatments, especially since individuals with HIV are now, generally, living much longer lives. They are concerned that TDF/FTC is associated with impaired renal function and weaker bones and anticipate that EVG/COBI/FTC/TAF will be associated with better results with respect to both.
- Treatment adherence is particularly important with regard to HIV treatment, as non-adherence can lead to drug class resistance. Once this occurs, it is necessary for the patient to embark on a different treatment regimen. Therefore, patients note that having many options available is of the utmost clinical importance.

Clinical Trials

The CDR systematic review included two phase 3 multi-centre, double-blind, double-dummy, active-controlled, non-inferiority trials (Study 104, N = 872; Study 111, N = 872), one phase 3 multi-centre, open-label, active-controlled, non-inferiority trial (Study 109, N = 1,443), and two multi-centre, open-label cohort studies (Study 112, N = 252; Study 106, N = 48). Studies 104 and 111 exclusively enrolled treatment-naive adults, whereas Study 109 enrolled only virologically suppressed adults who had been on an antiretroviral treatment (ART) regimen consisting of TDF/FTC + a third drug. Studies 112 and 106 evaluated the efficacy and safety of EVG/COBI/FTC/TAF in HIV-infected adults with mild to moderate kidney impairment and treatment-naive adolescents, respectively.

Outcomes

The following outcomes were defined a priori in the CDR systematic review protocol:

- Virologic success — percentage of patients with HIV-1 ribonucleic acid (RNA) < 50 copies/mL (FDA-defined snapshot algorithm)
- Resistance
- EuroQol 5-Dimenions Questionnaire 3 level (EQ-5D-3L) — change from baseline in EQ-5D-3L visual analogue scale and index scores

- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms (renal and bone systems).

The primary efficacy outcome for all studies was the percentage of patients with HIV-1 RNA < 50 copies/mL at week 48 (Studies 104, 111, and 109) or week 24 (Studies 112 and 106) using the FDA-defined snapshot algorithm.

Efficacy

- In Studies 104 and 111, EVG/COBI/FTC/TAF was non-inferior to EVG/COBI/FTC/TDF with respect to the percentage of patients with HIV-1 RNA < 50 copies/mL. The differences in proportions were:
  - Study 104: 1.0% (95% confidence interval [CI], −2.6 to 4.5) in the full analysis set (FAS) and –0.1% (95% CI, −2.2 to 2.1) in the per-protocol (PP) set
  - Study 111: 3.1% (95% CI, −1.0 to 7.1) in the FAS and 1.6% (95% CI, −1.1 to 4.4) in the PP analysis.
- In Study 109, results from the primary analysis demonstrated that significantly more patients who switched to EVG/COBI/FTC/TAF achieved HIV-1 RNA < 50 copies/mL at week 48 compared with those who stayed on their pre-existing TDF/FTC + a third drug regimen (difference in proportions 4.1%; 95% CI, 1.6 to 6.7; $P = 0.0002$).
- In Study 112, the primary analysis demonstrated that the virologic success rate at 24 weeks was 95.0% among adults who switched to EVG/COBI/FTC/TAF from their existing ARV regimen.
- In Study 106, the virologic success rate at 24 weeks was 91.3% for 23 ART-naive adolescents receiving EVG/COBI/FTC/TAF.

Harms (Safety and Tolerability)

- Across all five studies, at least 80% of patients in each trial experienced at least one treatment-emergent adverse event.
- Diarrhea, nausea, upper respiratory tract infections, and headache were the most common adverse events reported by patients receiving EVG/COBI/FTC/TAF.
- While the declines in kidney function (estimated glomerular filtration rate [eGFR]) and bone mineral density were less with EVG/COBI/FTC/TAF than with EVG/COBI/FTC/TDF, the observed changes are unlikely to be clinically significant in the short term and are of uncertain importance with respect to the risks for kidney failure or fracture in the long term.

Cost and Cost-Effectiveness

The manufacturer submitted a cost analysis comparing the drug cost of EVG/COBI/FTC/TAF with recommended ARV regimens for treatment-naive patients as outlined in the 2015 United States Department of Health and Human Services (DHHS) Guidelines, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (weighing 35 kg or more), with no known mutations associated with resistance to the individual components. These included: dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) (50/600/300 mg daily); DTG (50 mg daily) + TDF/FTC (200/300 mg daily); EVG/COBI/FTC/TDF (150/150/200/300 mg daily); raltegravir (RAL) (400 mg twice daily) + TDF/FTC (200/300 mg daily); and darunavir (DRV) (800 mg daily) boosted with 100 mg ritonavir + TDF/FTC (200/300 mg daily). The analysis considered drug costs only, as it was assumed that other resource-use components were equal between drugs. The assumption of similar efficacy and safety was based on clinical evidence from five phase 3 clinical trials.

The main limitation around the manufacturer's analysis centred on the lack of comparative clinical information for EVG/COBI/FTC/TAF versus other ARV regimens in adolescent patients and versus recommended ARV regimens for initial therapy in adult patients (other than EVG/COBI/FTC/TDF). Additionally, the manufacturer did not conduct a separate cost analysis for adolescent patients, which is limiting as there may be differences between the regimens used to treat adolescents and adults.

At the submitted confidential price of [redacted] per tablet, the daily drug cost of EVG/COBI/FTC/TAF is [redacted] or less expensive than other ARV regimens most often used in the treatment of HIV-1 infection in adolescent patients ($41.38 to $43.78 daily for other single-tablet regimens, including DTG/ABC/3TC, EFV/TDF/FTC, and FTC/RPV/TDF) and adult patients ($46.39 daily for EVG/COBI/FTC/TDF; and $41.38 to $55.57 daily for other DHHS-recommended regimens).

Other Discussion Points:
CDEC noted the following:

- EVG/COBI/FTC/TAF has the potential to be used for post-exposure prophylaxis, which is not an approved indication for this product.
- EVG/COBI/FTC/TAF is the only single-tablet regimen that is indicated for use in the treatment of adolescents with HIV-1 in Canada.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The included studies excluded patients who were co-infected with hepatitis B or hepatitis C.
- There is no clinical evidence for the safety and efficacy of EVG/COBI/FTC/TAF in treatment-experienced adolescent patients with HIV-1.

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.

February 17, 2016 Meeting

Regrets:
Four 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*.

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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