CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

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

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that emtricitabine/tenofovir alafenamide (FTC/TAF) be reimbursed for use in combination with other antiretrovirals (ARVs) (such as non-nucleoside reverse transcriptase inhibitors [NNRTIs] or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients aged 12 years and older (and weighing ≥ 35 kg), if the following condition is met:

Condition:
1. The cost of FTC/TAF should not exceed the cost of FTC/tenofovir disoproxil fumarate (TDF).

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) demonstrated that elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF was non-inferior to EVG/COBI/FTC/TDF for achieving viral load suppression in treatment-naive adults with HIV-1 infection after 48 weeks of treatment. Two RCTs demonstrated that switching to an FTC/TAF-based regimen was non-inferior to switching to an FTC/TDF-based regimen (with identical additional ARV drugs) for achieving viral load suppression in virologically suppressed adult patients at 48 weeks. 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 treatment-naive adolescents at 24 weeks. One open-label study demonstrated that treatment with EVG/COBI/FTC/TAF in patients with reduced kidney function was associated with a virologic success rate of 95.0% among adults who switched from their existing ARV regimen after 24 weeks of treatment.
2. At the submitted price ($28.57 per tablet), FTC/TAF is similar in cost to other commonly used treatment regimens for adults and adolescents with HIV-1 infection.

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

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Background:
Emtricitabine/tenofovir alafenamide (FTC/TAF) has a Health Canada indication for use in combination with other ARVs (such as NNRTIs or protease inhibitors) for the treatment of HIV-1 infection in adult and pediatric patients aged 12 years and older (and weighing ≥ 35 kg).

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of FTC/TAF for HIV-1 infection, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals with HIV-1 infection.

Patient Input Information:
One patient group, the Canadian Treatment Action Council, responded to the CDR call for patient input. Information was gathered via a national consultation webinar, a survey, and from survey data used in patient submissions for other HIV treatments.

- 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 with HIV indicated concerns about the increased risk of comorbidities such as accelerated aging; inflammation; kidney, liver, and cardiovascular disease; and bone fractures.
- One survey respondent expressed enthusiasm about switching from a FTC/TDF regimen to one with FTC/TAF "if it is less harmful over long periods," although the individual expected the safety profiles to be similar.
- 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 three phase 3, multi-centre, double-blind, double-dummy, active-controlled, non-inferiority trials (study 104, N = 872; study 111, N = 872; study 1089, N = 663); 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 studies 109 and 1089 enrolled only virologically suppressed adults who had been on an FTC/TDF-based regimen; i.e., EVG/COBI/FTC/TAF or FTC/TAF + 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. The inclusion of studies evaluating the FTC/TAF-based antiretroviral therapy (ART) regimen EVG/COBI/FTC/TAF was based on evidence from two phase 1bioequivalence studies (study 1472 and study 1473). The FTC and TAF components of the FTC/TAF-based backbone alone or in combination with EVG + COBI were found to be bioequivalent to the FTC and TAF components of EVG/COBI/FTC/TAF.

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Outcomes

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

- Virologic success — percentage of patients with viral load < 50 copies/mL (FDA-defined snapshot algorithm)
- Resistance
- Health-related quality of life
- Adherence
- 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, 109, and 1089) or week 24 (studies 112 and 106) using the FDA-defined snapshot algorithm.

Efficacy

- In studies 104, 111, 109, and 1089, the FTC/TAF-based regimens (EVG/COBI/FTC/TAF or FTC/TAF + a third drug) were non-inferior to the FTC/TDF-based regimens (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 set
  - Study 109: 4.1% (95% CI, 1.6 to 6.7) in the FAS and 0.3% (95% CI not reported) in the PP set
  - Study 1089: 1.3% (95% CI, –2.5 to 5.1) in the FAS (no PP set data provided).
- 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 regimen.
- In study 106, the virologic success rate at 24 weeks was 91.3% for 23 ART-naive adolescents receiving EVG/COBI/FTC/TAF.
- Across studies 104 and 111, a total of seven (0.8%) and five (0.6%) patients receiving an FTC/TAF-based regimen and an FTC/TDF-based regimen, respectively, who experienced virologic failure, developed primary genotypic resistance through week 48. In study 109, one patient who switched to the EVG/COBI/FTC/TAF group developed resistance to FTC through week 48. In study 1089, one (0.3%) patient receiving an FTC/TAF-based regimen and no patients receiving an FTC/TDF-based regimen developed genotypic resistance through week 48. In studies 112 and 106, through week 48, no patients receiving an FTC/TAF-based regimen developed new resistance or mutations that were not already present at baseline.
- There were no differences in health-related quality of life among patients receiving an FTC/TAF-based regimen or an FTC/TDF-based regimen comparator.
- Across all studies, at least 77% of patients in each treatment arm achieved adherence rates of ≥ 95%.

Harms (Safety and Tolerability)

- Across all five studies, at least 80% of patients in each trial experienced at least one treatment-emergent adverse event.

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- Diarrhea (9% to 19%), nausea (< 5% to 23%), upper respiratory tract infections (9% to 17%), and headache (7% to 17%) appeared to be the most common adverse events reported by patients receiving FTC/TAF-based regimens.
- While the declines in kidney function (estimated glomerular filtration rate [eGFR]) and bone mineral density were less with FTC/TAF-based regimens than with FTC/TDF-based regimens, 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 submitted price per 200 mg/10 mg or 200 mg/25 mg tablet of FTC/TAF, and daily cost based on the approved dosage, is $28.57. The manufacturer submitted a cost analysis comparing all recommended and alternative ARV regimens as outlined in the 2015 United States Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. FTC/TAF and FTC/TDF were considered to have similar efficacy and safety based on the available trial evidence. The manufacturer's approach assumes that FTC/TAF will supplant FTC/TDF; hence, the daily cost of FTC/TDF-containing regimens was compared with either FTC/TDF or FTC/TAF.

CDR noted the following key limitations of the analysis:

- There was no comparative evidence in adolescents for FTC/TAF- versus FTC/TDF-based regimens. Consequently, there is uncertainty regarding the assumption that the clinical effectiveness and harms of FTC/TAF and FTC/TDF are similar, as well as the appropriateness of a cost (rather than cost-effectiveness) analysis in this population.
- According to clinical expert input, FTC/TAF may be used in clinical practice as initial therapy in combination with either dolutegravir, raltegravir, ritonavir-boosted darunavir (DRV)/r, or DRV/COBI. However, there are no clinical data from treatment-naive patients comparing FTC/TAF and FTC/TDF other than in EVG/COBI-based regimens. Hence, there is uncertainty regarding the comparative clinical effectiveness and safety of FTC/TAF and FTC/TDF used as part of initial regimens that do not contain EVG/COBI, as well as the appropriateness of a cost (rather than cost-effectiveness) analysis for these regimens.

The submitted price of FTC/TAF is less by $0.51 than the publicly available price of FTC/TDF on the Ontario Drug Benefit formulary, but $0.87 higher than the publicly available price of FTC/TDF on the Saskatchewan Drug Benefit formulary (the lowest listed price in Canada identified by CDR). CDR noted that FTC/TDF- and FTC/TAF-containing regimens are not the lowest-cost DHHS-recommended or alternative regimens available in Canada.

Other Discussion Points:

CDEC noted the following:

- FTC/TAF has the potential to be used for pre-exposure prophylaxis, which is not an approved indication for this product.
- None of the included studies addressed switching therapies for a treatment-experienced patient with a non-suppressed viral load. The use of FTC/TAF in these patients would be guided by the results of genotypic resistance testing.
- The short-term toxicity profile (bone mineral density, glomerular filtration rate) of the drugs in FTC/TAF suggests that there may be some safety benefits compared with FTC/TDF. However, the long-term effects are unknown.

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July 20, 2016 Meeting

Regrets: None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement 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 not requested the removal of confidential information.

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