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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE (ODEFSEY — GILEAD SCIENCES CANADA INC.)

Indication: HIV-1 Infection

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) be reimbursed as a complete regimen for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) who have no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine (FTC) and with a viral load ≤ 100,000 copies/mL, if the following conditions are met:

Conditions:

- The cost of FTC/RPV/TAF should not exceed the cost of FTC/RPV/tenofovir disoproxil fumarate (TDF) or the individual components of FTC/RPV/TAF used in combination.
- Reimburse in a similar manner to other single tablet regimens (STRs) for the treatment of HIV-1 infection.

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EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE (ODEFSEY — GILEAD SCIENCES CANADA INC.)

Indication: HIV-1 Infection

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) be reimbursed as a complete regimen for the treatment of adults infected with HIV type 1 (HIV-1) who have no known mutations associated with resistance to the non-nucleoside reverse-transcriptase inhibitor (NNRTI) class, tenofovir or FTC and with a viral load ≤ 100,000 copies/mL, if the following conditions are met:

Conditions:

- The cost of FTC/RPV/TAF should not exceed the cost of FTC/RPV/ tenofovir disoproxil fumarate (TDF) or the individual components of FTC/RPV/TAF used in combination.
- Reimburse in a similar manner to other single tablet regimens (STRs) for the treatment of HIV-1 infection.

Reasons for the Recommendation:

1. Two phase IIIb studies demonstrated that switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1160; N = 881) or efavirenz (EFV)/TDF/FTC (Study 1216; N = 632) in virologically suppressed patients (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) with preserved renal function (estimated glomerular filtration rate [eGFR] > 50 mL/min) resulted in an improved safety profile with respect to renal function and bone density.
2. In Study 1160 and Study 1216, patients who switched to FTC/RPV/TAF had similar rates of virologic success at 48 weeks as patients who were maintained on their previous regimen, meeting the pre-specified non-inferiority criteria.
3. One randomized, open-label, single-dose study (Study 1159; N = 96) with HIV-negative volunteers with an eGFR > 70 mL/min demonstrated that FTC and TAF had comparable bioavailability when administered as elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF or as FTC/RPV/TAF. The same study demonstrated that RPV had comparable bioavailability when administered as a single tablet or as FTC/RPV/TAF.
4. At the submitted price of $42.37 per tablet ($42.37 daily), FTC/RPV/TAF is cost-saving compared with the sum of the costs of its individual components: RPV ($15.14 daily) and FTC/TAF ($28.57 daily). The submitted price of FTC/RPV/TAF is lower than the current list price of its TDF-containing counterpart, FTC/RPV/TDF ($44.11 daily).

Of Note:

- CDEC noted that FTC/RPV/TAF is likely to supplant FTC/RPV/TDF for the treatment of HIV-1 infection.
- CDEC noted that the cost of antiretroviral regimens may differ across the jurisdictions that participate in the CADTH Common Drug Review (CDR) process.

Discussion Points:

- CDEC noted that the improved safety profile experienced by patients in Studies 1160 and 1216 included less bone loss at the hip and spine and more favourable renal toxicity outcomes, including reduced proteinuria, albuminuria, and tubular proteinuria; however, the long-term effects of switching to FTC/RPV/TAF on clinical outcomes (e.g., fractures and end-stage renal disease) are unknown.
- CDEC recognized that six phase III studies that did not include treatment with FTC/RPV/TAF were included in the manufacturer's submission as supportive studies. These studies were previously reviewed by CADTH in the CDR submissions for Genvoya, Descovy, and Edurant. These submissions received recommendations from CDEC to reimburse or reimburse with a condition.

Background:

FTC/RPV/TAF is a three-drug STR product consisting of the following:

- 25 mg RPV, an NNRTI
- 200 mg FTC, a nucleos(t)ide reverse-transcriptase inhibitor (NRTI)
- 25 mg TAF, an NRTI

FTC/RPV/TAF is indicated as a complete regimen for the treatment of adults infected with HIV-1 who have no known mutations associated with resistance to the NNRTI class, tenofovir or FTC, and with a viral load of ≤ 100,000 copies per mL. The recommended dose of FTC/RPV/TAF is one tablet taken orally once daily with food. The product monograph states that FTC/RPV/TAF must be taken with a meal to obtain optimal absorption of the RPV.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a review of manufacturer-provided information on the clinical evidence (bioequivalence, efficacy, and safety) for FTC/RPV/TAF, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients living with HIV infection.

Patient Input Information

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

- HIV infection can lead to 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.
- Nonadherence to HIV treatment can lead to drug class resistance. If this occurs, patients must embark on a different treatment regimen. Therefore, patients note that once-daily regimens associated with improved adherence and having several treatment options available are of the utmost clinical importance.
- Patients noted that TAF is associated with fewer renal issues and a reduction in the loss of bone mineral density compared with TDF. This improvement in the adverse event profile was considered to be important for patients, who require the use of HIV antiviral treatment for their lifetime.

Bioequivalence

The manufacturer's submission included a summary of one pivotal bioequivalence study (Study 1159 [N = 96]) that compared the individual components of FTC/RPV/TAF against the individual components of two reference products: EVG/COBI/FTC/TAF and RPV. Study 1159 was a randomized single-dose, open-label, three-way, six-sequence crossover phase I study that enrolled healthy HIV-negative adults with a creatinine clearance ≥ 70 mL/min. Patients were randomized to all three of the following treatments in one of six treatment sequences:

- FTC 200 mg, RPV 25 mg, and TAF 25 mg as FTC/RPV/TAF
- RPV 25 mg as Edurant; or
- EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg as Genvoya.

The primary end points were the pharmacokinetic (PK) parameters, area under the plasma concentration versus time curve (AUC), both from time 0 to the last quantifiable concentration (AUC_{last}) and extrapolated to infinity (AUC_{inf}), and the maximum plasma concentration (C_{max}). FTC and TAF administered as FTC/RPV/TAF met the primary end points of the study and demonstrated bioequivalence to EVG/COBI/FTC/TAF and RPV under fed conditions. Similarly, RPV administered as FTC/RPV/TAF demonstrated

bioequivalence to RPV. The results of the bioequivalence study were used to bridge the efficacy and safety data of RPV (Edurant), EVG/COBI/FTC/TAF (Genvoya), and FTC/RPV/TDF (Complera) to support market authorization of FTC/RPV/TAF.

Clinical Trials

The efficacy data provided in the manufacturer's submission were derived from seven phase III studies and two phase IIIb studies. The phase III randomized controlled trials were all conducted using products other than FTC/RPV/TAF such as the following: four trials conducted using EVG/COBI/FTC/TAF, including two studies comparing EVG/COBI/FTC/TAF with EVG/COBI/FTC/TDF in treatment-naive patients (Study 104 [N = 872] and Study 111 [N = 872]), one trial comparing EVG/COBI/FTC/TAF against TDF/FTC plus a third drug (Study 109 [N = 1443]) in adults who were virologically supressed, and one uncontrolled trial conducted in adults with mild to moderate renal failure (Study 112 [N = 248]); two phase III studies comparing RPV with EFV in combination with FTC/TDF (ECHO [N = 694]) or FTC/TDF, zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC) (THRIVE [N = 680]); and one phase III switching study comparing FTC/RPV/TDF with the patient's prior treatment regimen (SPIRIT [N = 476]). The majority of the phase III studies that were included in the review have been previously reviewed by CADTH in the CDR submissions for EVG/COBI/FTC/TAF, FTC/TAF, and RPV. All three of these reference products received recommendations from CDEC to list or list with a condition. The two phase IIIb studies evaluated switching to FTC/RPV/TAF from FTC/RPV/TDF (Study 1216 [N = 632]) or EFV/TDF/FTC (Study 1160 [N = 881]).

Outcomes

The manufacturer's submission included the following outcomes:

- virologic success — percentage of patients with viral load < 50 copies per mL (FDA-defined snapshot algorithm)
- percentage of patients with viral load < 20 copies per mL
- percentage change from baseline in hip and spine bone mineral density (BMD)
- renal adverse events.

The primary efficacy end point was virologic success in both Studies 1160 and 1216.

Efficacy

FTC/RPV/TAF versus FTC/EFV/TDF (Study 1160)

- Switching to FTC/RPV/TAF was noninferior to remaining on treatment with FTC/EFV/TDF for virologic success at 48 weeks. The proportion of patients with virologic success at 48 weeks was 90.0% and 92.0% respectively (risk difference [RD]: −2.0% [95% CI, −5.9 to 1.8]).
- The proportion of patients with HIV-1 RNA < 20 copies per mL at 48 weeks were 86.5% with FTC/RPV/TAF and 90.4% with FTC/EFV/TDF (RD: −3.9% [95% CI, −8.2 to 0.5]).
- No patients developed resistance to FTC/RPV/TAF and one patient developed resistance to FTC/EFV/TDF.

FTC/RPV/TAF versus FTC/RPV/TDF (Study 1216)

- Switching to FTC/RPV/TAF was noninferior to remaining on treatment with FTC/RPV/TDF for virologic success at 48 weeks. The proportion of patients with virologic success at 48 weeks was 93.7% with FTC/RPV/TAF and 93.9% with FTC/RPV/TDF (RD: −0.3% [−4.2% to 3.7%]).
- The proportion of patients with HIV-1 RNA < 20 copies per mL at 48 weeks were 91.8% with FTC/RPV/TAF and 90.4% with FTC/RPV/TDF (RD: 1.4% [−3.2% to 6.0%]).
- No patients developed resistance to FTC/RPV/TAF or FTC/RPV/TDF.

Harms (Safety and Tolerability)

- Percentage change from baseline in hip and spine BMD were pre-specified key secondary end points in both Studies 1160 and 1216. At the 48-week interim analysis, both studies demonstrated a statistically significant improvement from baseline in BMD at the hip and spine in patients who switched to FTC/RPV/TAF compared with those who continued to be treated

with FTC/RPV/TDF or FTC/EFV/TDF ($P < 0.001$ for spine and hip BMD in both studies). Mean (standard deviation) percentage changes from baseline to 48 weeks in BMD were:

  - Hip BMD: 1.28% (2.38%) with FTC/RPV/TAF and −0.13% (2.49%) with FTC/EFV/TDF in Study 1160; 1.04% (1.94%) with FTC/RPV/TAF and −0.25% (2.08%) with FTC/RPV/TDF in Study 1216.
  - Spine BMD: 1.65% (3.32%) with FTC/RPV/TAF and −0.05% (2.91%) with FTC/EFV/TDF in Study 1160; 1.61% (3.44%) for FTC/RPV/TAF and 0.08% (2.96%) with FTC/RPV/TDF in Study 1216.

- There was a statistically significant difference in change from baseline in eGFR favouring FTC/RPV/TAF compared with FTC/RPV/TDF at 48 weeks in Study 1216. In contrast, there was a statistically significant decrease in eGFR for patients who switched from FTC/EFV/TDF to FTC/RPV/TAF at 48 weeks in Study 1160. The decrease in eGFR is likely associated with the initiation of treatment involving RPV, which is not a component of FTC/EFV/TDF, and is known to reduce tubular secretion of creatinine.
- Compared with FTC/EFV/TDF and FTC/RPV/TDF, patients who switched to FTC/RPV/TAF demonstrated statistically significant reductions in proteinuria, albuminuria, and tubular proteinuria.

Cost and Cost-Effectiveness

The submitted price of FTC/RPV/TAF is $42.37 per 200/25/25 mg tablet, or $42.37 daily. The manufacturer submitted a cost analysis comparing FTC/RPV/TAF STR with all alternative antiretroviral regimens as outlined in the 2016 US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 infected Adults and Adolescents. At the submitted daily price, FTC/RPV/TAF is less costly than the sum of its individual components RPV ($15.14 daily) and FTC/TAF ($28.57 daily). This would result in savings of $1.34 daily per patient. FTC/RPV/TAF is also less costly than other DHHS-alternative STRs, with daily cost savings ranging from $1.74 (compared with FTC/RPV/TDF) to $2.19 (compared with EFV/FTC/TDF).

CDR noted the following with the analysis:

- According to the clinical expert consulted for the review, most patients favour STRs over multi-tablet regimens owing to convenient administration. As a result, CDR considered the costs of all regimens recommended by the US DHHS Guidelines, including the five available STRs, and noted that FTC/RPV/TAF was less costly than most regimens. While the availability of FTC/RPV/TAF has the potential to displace the market share from other STR products, clinical expert feedback suggested that FTC/RPV/TAF is not likely to be favoured compared with other DHHS-recommended regimens but is most likely to displace its TDF-containing STR counterpart, FTC/RPV/TDF. CDR also noted that while fixed-dose regimens may be preferred by most patients, the products in this new STR may prevent the realization of cost savings from generic entrants as individual drug patents expire. The patent for TDF is expected to expire in 2018; yet, savings which could be achieved from the potential generic substitution will not be realized for TDF-containing fixed-dose regimens. The potential for cost savings is further reduced by the introduction of TAF-based co-formulations, which may displace use of TDF-based combination products.

At the submitted daily price of $42.37 per tablet, FTC/RPV/TAF is less costly than the sum of its individual components RPV and FTC/TAF, resulting in savings of $1.34 daily per patient. In addition, FTC/RPV/TAF is less costly than other DHHS-alternative STRs, including FTC/RPV/TDF ($44.11 daily). In comparison with DHHS-preferred STRs, the daily cost of FTC/RPV/TAF is similar to DTG/ABC/3TC ($42.50 daily) and less costly than other DHHS-preferred STRs ($46.39 to $47.22 daily).

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 19, 2017 Meeting

Regrets:

None

Conflicts of Interest:

None