CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (BIKTARVY — GILEAD SCIENCES CANADA, INC.)
Indication: As a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of Biktarvy.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) should be reimbursed for the treatment of HIV-1 in adults with no known substitution associated with resistance to the individual components, if the following condition is met:

Condition
The total cost of treatment with BIC/FTC/TAF should not exceed the total drug plan cost of treatment with the least costly alternative regimen for the treatment of HIV-1.

Service Line: CADTH Drug Reimbursement Recommendation
Version: Final
Publication Date: October 2018
Report Length: 8 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (BIKTARVY — Gilead Sciences Canada, Inc.)

Indication: As a complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of Biktarvy.

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) should be reimbursed for the treatment of HIV-1 in adults with no known substitution associated with resistance to the individual components, if the following condition is met:

Condition:

The total cost of treatment with BIC/FTC/TAF should not exceed the total drug plan cost of treatment with the least costly alternative regimen for the treatment of HIV-1.

Reasons for the Recommendation:

1. In two randomized controlled trials (RCTs) conducted in treatment-naive patients with HIV-1, BIC/FTC/TAF was noninferior to abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) and to DTG + FTC/TAF in achieving virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. In three RCTs conducted in treatment-experienced patients with virologically suppressed HIV-1, BIC/FTC/TAF was noninferior to continuing treatment with (1) ABC/DTG/3TC, (2) ritonavir (RTV)- or cobicistat (COBI or C)-boosted atazanavir (ATV) or darunavir (DRV) + either FTC/tenofovir disoproxil fumarate (TDF) or ABC/3TC, (3) elvitegravir (E)/C/FTC/TAF, (4) E/C/FTC/TDF, or (5) ATV + RTV + FTC/TDF, in terms of the proportion of patients experiencing virologic failure (HIV-1 RNA ≥ 50 copies/mL) at week 48. Harms were similar among treatment groups, and surrogate outcomes for renal and bone safety were similar at week 48.

2. An indirect treatment comparison (ITC) of safety and efficacy submitted by the manufacturer did not provide compelling evidence that treatment with BIC/FTC/TAF differs from other currently available treatments.

3. The daily cost of BIC/FTC/TAF is higher than that of most TDF-based regimens currently reimbursed by drug plans.

Implementation Considerations:

The committee noted that several jurisdictions have specific reimbursement criteria for drugs for the treatment of HIV-1 and that they may wish to reimburse BIC/FTC/TAF in a manner similar to other HIV-1 treatment regimens.

Discussion Points:

- The committee discussed that there is no unmet need for another antiretroviral (ARV) regimen for the treatment of HIV-1, given the numerous single- and double-tablet regimens available, and that appropriate regimens to manage patient-specific needs (e.g., avoidance of drug–drug interactions or adverse events [AEs]) are easily identified, given the large number of available regimens.
- The committee noted that DTG, another integrase strand transfer inhibitor (INSTI) that is included in a number of regimens recommended by the US Department of Health and Human Services, should be avoided in women of childbearing potential who are trying to become pregnant, according to a Health Canada safety alert. The committee further discussed that the evidence for this AE comes from an ongoing observational study in a low-income country. The safety of bictegravir in pregnancy is currently unknown.
- The committee discussed that only 48-week data for all five of the trials were available and that this is a relatively short duration, given the chronic nature of treatment.

Background:

BIC/FTC/TAF has a Health Canada indication as a complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of BIC/FTC/TAF. Bictegravir is an INSTI, and both emtricitabine and tenofovir alafenamide are nucleoside reverse transcriptase inhibitors (NRTIs). BIC/FTC/TAF is available as a fixed-dose combination (50 mg/200 mg/25 mg), and the Health Canada–approved dosage is one tablet taken orally once daily, with or without food.

Summary of Evidence Considered by CDEC:

The committee considered the following information prepared by CADTH Common Drug Review (CDR): a systematic review of RCTs of BIC/FTC/TAF (50 mg/ 200 mg/25 mg) and a critique of the manufacturer-provided ITC and manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with HIV-1, and from patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Treatment Action Council, provided input for this submission. Patient perspectives were obtained from a consultation workshop in Toronto and from survey data collected for the patient submission on the DTG/rilpivirine (RPV) combination product. The following is a summary of key input from the perspective of the patient group:

- Patients living with HIV infection are concerned with what they refer to as "accelerated aging," including greater risk of bone fractures and of kidney, liver, and cardiovascular disease. Patient group input noted that patients would like new treatments that reduce the risk of long-term negative effects on bone density, the liver, and the kidneys.
- In addition to mental and physical effects of HIV and its treatment, patients also experience stigma, discrimination, and related stress.
- Patients noted that that their treatments (both old and new) were effective at suppressing their viral load; however, there was a sense that people living with HIV have varying responses to treatments, including significant side effects and tolerability issues. Thus, the patient input emphasized that having the maximum number of possible treatment options available is of clinical importance.
- BIC/FTC/TAF was expected to have the benefit of being a smaller pill that could be taken with or without food, thus having the potential to increase adherence, which patients noted is important for treatments to be effective.

Clinical Trials

The systematic review included two phase III trials in treatment-naive patients (Study 1489, N = 631, and Study 1490, N = 657) and three phase III switch trials in treatment-experienced patients (Study 1844, N = 567; Study 1878, N = 578; and Study 1961, N = 472). Study 1489 and 1490 were double-blind, randomized (1:1), noninferiority trials; the active comparator for Study 1489 was ABC/DTG/3TC (600 mg/50 mg/300 mg), while the comparator for Study 1490 was DTG (50 mg) + FTC/TAF (200 mg/25 mg). Both Study 1489 and 1490 were ongoing to 144 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week-48 visit or had prematurely discontinued study drugs before their week-48 visit.

Studies 1844, 1878, and 1961 were also double-blind, randomized (1:1), noninferiority trials; randomization was stratified by prior baseline regimen (patients were randomized to switch to BIC/FTC/TAF or to stay on baseline regimens [SBR]). The active comparator for 1844 was SBR of ABC/DTG/3TC (600 mg/50 mg/300 mg). The active comparator for Study 1878 was SBR of RTV- or COBI-boosted ATV or DRV + either FTC/TDF or ABC/3TC. The active comparator for Study 1961 was SBR of E/C/FTC/TAF (150 mg/150 mg/200 mg/10 mg), E/C/FTC/TDF (150 mg/150 mg/200 mg/300 mg), or ATV (300 mg) + RTV (100 mg) + FTC/TDF (200 mg/300 mg). Studies 1844, 1878, and 1961 were ongoing to 96 weeks, with the cut point for the manufacturer-provided data being when all randomized subjects had completed the week-48 visit or had prematurely discontinued study drugs before their week-48 visit.

Outcomes

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

- Virologic success: Proportion of patients with HIV-1 RNA < 50 copies/mL, as determined by the US FDA–defined snapshot algorithm (primary outcome for Studies 1489 and 1490; secondary outcome for Studies 1844, 1878, and 1961)
- Virologic failure: Proportion of patients with HIV-1 RNA ≥ 50 copies/mL, as determined by the US FDA–defined snapshot algorithm (primary outcome for Studies 1844, 1878, and 1961; secondary outcome for Studies 1489 and 1490)
- Health-related quality of life (HRQoL)
- Adherence to medication
- Resistance
- Serum creatinine and estimated glomerular filtration rate (eGFR)
- Bone mineral density (BMD).

Efficacy

Treatment-Naive

In Study 1489 and 1490, 92% versus 93% and 89% versus 92% of patients in BIC/FTC/TAF versus ABC/DTG/3TC or DTG + FTC/TAF groups achieved the primary end point of HIV-1 RNA < 50 copies/mL at week 48. Based on these data, BIC/FTC/TAF was noninferior to the active comparators (ABC/DTG/ 3TC and DTG + FTC/TAF) based on the noninferiority margin of –12%, with between-treatment differences in the full analysis set (FAS) of Studies 1489 and 1490 of –0.6% (95% confidence interval [CI], –4.8% to 3.6%) and –3.5% (95% CI, –7.9% to 1.0%), respectively. Noninferiority was confirmed in the per-protocol (PP) population in both trials.

- HRQoL was measured using the Short Form (36) Health Survey (SF-36) in both studies but provided for Study 1489 only. No statistically significant between-treatment differences in the SF-36 physical component summary and mental component summary were reported. This was only an exploratory outcome.
- In Study 1489 and 1490, mean adherence was [redacted] in BIC/FTC/TAF versus ABC/DTG/3TC or DTG + FTC/TAF groups, respectively.

Treatment-Experienced/Switch

- In Study 1844, 1.1% and 0.4% of patients in the BIC/FTC/TAF and ABC/DTG/3TC groups, respectively, had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (between-treatment per cent difference at 48 weeks: 0.7%; 95% CI, –1.0% to 2.8%). The results from the PP analysis were consistent with those of the FAS analysis.
- In Study 1878, 1.7% of patients in the BIC/FTC/TAF group and in the SBR group had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (between-treatment per cent difference at 48 weeks: 0.0%; 95% CI, –2.5% to 2.5%). The results from the PP analysis were consistent with those of the FAS analysis.
- In Study 1961, 1.7% of patients in the BIC/FTC/TAF group and in the SBR group had HIV-1 RNA ≥ 50 copies/mL at 48 weeks. These results met the pre-specified noninferiority margin of 4% (between-treatment per cent difference at 48 weeks: 0.0%; 95% CI, –2.9% to 2.9%). The results from the PP analysis were consistent with those of the FAS analysis.
- HRQoL was measured using the SF-36 in Study 1844 only. No statistically significant differences in the SF-36 physical component summary and mental component summary were reported between the BIC/FTC/TAF group and the ABC/DTG/3TC group.

- Mean adherence was [redacted] in the BIC/FTC/TAF and ABC/DTG/3TC groups, respectively, in Study 1844, and [redacted] in the BIC/FTC/TAF and SBR groups, respectively, in Study 1961. Adherence was reported only for the BIC/FTC/TAF group in Study 1878; mean adherence in the BIC/FTC/TAF group was [redacted].

Harms (Safety)

Treatment-Naive

- Overall AEs were similar in Study 1489 (84.4% and 89.8% of patients in the BIC/FTC/TAF and ABC/DTG/3TC groups, respectively) and in Study 1490 (82.5% and 83.7% of patients in the BIC/FTC/TAF and DTG + FTC/TAF groups, respectively).
- There were no deaths in Study 1489. There were three deaths in Study 1490 (BIC/FTC/TAF group, n = 1 and DTG + FTC/TAF group, n = 2). None of the deaths were deemed related to treatment.
- A small proportion of patients withdrew from the trials due to AEs (Study 1489: BIC/FTC/TAF, 0, ABC/DTG/3TC, 4 [1.3%]; Study 1490: BIC/FTC/TAF, 5 [1.6%], DTG + FTC/TAF 1 [0.3%]).
- No patients developed treatment-emergent drug resistance in either Study 1489 or 1490.
- In both trials, serum creatinine increased slightly from baseline to week 48 in both groups; however, week-48 serum creatinine was still within normal range. In both studies, eGFR decreased from baseline to week 48 in both groups, slightly more in the comparator arms containing DTG.
- In Study 1489, both treatment groups experienced small declines in hip and spine BMD from baseline to week 48 that were not clinically meaningful. BMD was not measured in Study 1490.

Treatment-experienced/switch

- In the treatment-experienced/switch trials, the majority of the study populations experienced at least one AE (65.8% to 80.3%). AEs were balanced across treatment groups.
- There were two deaths in Study 1844 (both in BIC/FTC/TAF group), two deaths in Study 1878 (one in each of the BIC/FTC/TAF and SBR groups), and one death in Study 1961 (SBR group); none of the deaths were deemed related to treatment.
- A small proportion of patients withdrew from the study due to AEs (Study 1844: BIC/FTC/TAF 6 [2.1%], ABC/DTG/3TC 2 [0.7%]; Study 1878: BIC/FTC/TAF 2 [0.7%], SBR 1 [0.3%]; Study 1961: BIC/FTC/TAF 0, SBR: 0).
- No patients in Study 1844 developed treatment-emergent drug resistance. In Study 1878, one patient in the SBR group (on a regimen of RTV-boosted DRV + ABC/3TC) developed L74V in reverse transcriptase. In Study 1961, one patient in the SBR group (patient taking E/C/FTC/TAF) developed M184M/I/V.
- Change in serum creatinine from baseline to 48 weeks in all three studies increased minimally and with similar magnitude in all treatment groups. Small but clinically insignificant changes in eGFR from baseline to week 48 were observed in treatment groups across the trials.
- BMD was measured in Study 1844 but not in Study 1878 or Study 1961. No clinically meaningful changes in BMD at the hip or spine were observed.

Indirect Treatment Comparisons

[redacted]

[redacted] However, given a number of limitations (including [redacted]), the NMA did not provide compelling evidence that the safety and efficacy of BIC/FTC/TAF [redacted] differs from its comparators.

Cost and Cost-Effectiveness

BIC/FTC/TAF (Biktarvy) is an oral single-tablet regimen indicated for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of BIC/FTC/TAF. It is available as a fixed-dose combination of 50 mg of B, 200 mg of FTC, and 25 mg of TAF tablet, and it is taken once daily. At the manufacturer-submitted price of $39.22 per tablet, the annual cost of treatment is approximately $14,315 per patient.

The manufacturer submitted a Markov economic model, which evaluated health outcomes in terms of quality-adjusted life-years (QALYs) gained. The model compared the cost-effectiveness of BIC/FTC/TAF with available ARV regimens recommended for initial therapy by the US Department of Health and Human Services guidelines and aligned with market research claims data within Canada. These comparators included DTG/ABC/3TC (Triumeq), FTC/TAF + DTG (Descovy + Tivicay), E/C/FTC/TAF (Genvoya), and FTC/TAF + raltegravir (Descovy + Isentress). The economic model consisted of six health states (five core health states and death) based on CD4 cell count ranges, as recorded in the BIC/FTC/TAF pivotal trials. Transition probabilities between different health states for BIC/FTC/TAF were derived from the pivotal trials for BIC/FTC/TAF, and relative effects of comparator treatments were based on the results of an NMA. Utility values were derived from the literature. The cycle length for the analysis was 13 weeks for the first four cycles and then 26 weeks for the remainder of the model. The model used a lifetime horizon (up to 70 years from model initiation) in the base case. All costs and outcomes were discounted at an annual rate of 1.5%, and the analysis was conducted from the perspective of the Canadian publicly funded health care system. The manufacturer reported that BIC/FTC/TAF was less costly and led to better outcomes (gains in QALYs) over the lifetime when compared with other treatments. Based on sequential analysis of the manufacturer's base case, BIC/FTC/TAF was considered a cost-effective option, as it dominated (i.e., had lower costs and greater QALYs) all other treatments included as comparators in the analysis.

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

- The model did not reflect the individualized nature of HIV treatment and may have overestimated BIC/FTC/TAF cost savings.
- The model consisted of health states based on defined CD4 cell count ranges. The clinical expert consulted by CDR indicated that CD4 cell counts have much less prognostic value in predicting outcomes once patients have started treatment on an ARV and virologic suppression has been achieved (i.e., number of copies of the virus < 50 copies/mL). By using CD4-based health states, the manufacturer's model may have overestimated the true efficacy of the included ARV treatments.
- The relative efficacy for the comparators was based on an NMA that was conducted using studies of treatment-naive patients only, though the manufacturer's target population is for both treatment-naive and -experienced patients. The CDR Clinical Review team identified several limitations in the NMA and concluded that the NMA failed to provide compelling evidence that the safety and efficacy of BIC/FTC/TAF differs from its comparators as initial treatment of HIV-1.
- The manufacturer's economic submission did not consider relevant comparators (e.g., RPV/FTC/TDF, Complera). The manufacturer did not provide justification as to why treatments such as RPV/FTC/TDF (or other NRTI-based regimens) were excluded despite having been included in the NMA.

Given the limitations with the structure of the submitted model, CDR did not undertake reanalyses based on an uncertain model structure.

At a daily cost of $39.22, BIC/FTC/TAF is less expensive than the publicly available prices of the comparator treatments identified by the manufacturer — Triumeq ($43.20), Descovy + Tivicay ($45.60), Genvoya ($46.39) and Descovy + Isentress ($54.16), but BIC/FTC/TAF is more expensive than most TDF-based regimens (e.g., Truvada generic + Isentress, [$35.36], Truvada generic + Tivicay [$26.80]) and several of the NRTI-boosted regimens.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 19, 2018 Meeting:

Regrets:

Two CDEC member(s) did not attend.

Conflicts of Interest:

None