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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (Symtuza — Janssen Inc.)
Indication: Treatment of HIV type 1 (HIV-1) infection.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of D/C/F/TAF, if the following condition is met:

Condition

- The total cost of treatment with D/C/F/TAF should not exceed the total drug-plan cost of treatment with the least costly alternative triple or quadruple single-tablet regimen

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of D/C/F/TAF, if the following condition is met:

Condition

- The total cost of treatment with D/C/F/TAF should not exceed the total drug plan cost of treatment with the least costly alternative triple or quadruple single-tablet regimen (STR).

Reasons for the Recommendation

1. Two multi-centre, double-blind, noninferiority, randomized controlled trials (RCTs) (GS-US-299-0102 [N = 153] and AMBER [N = 725]) demonstrated that D/C/F/TAF was noninferior to co-administration of the individual components of D/C and F/tenofovir disoproxil fumarate (TDF) for the proportion of patients achieving virologic success (i.e., HIV-1 RNA < 50 copies/mL) in treatment-naive patients, up to week 48 of treatment. One multi-centre, open-label, noninferiority RCT (EMERALD, N = 1,141) demonstrated that switching to D/C/F/TAF was noninferior to remaining on treatment with a boosted protease inhibitor (bPI) plus F/TDF in terms of the proportion of patients without virologic rebound up to 48 weeks of treatment in patients with prior treatment experience and virologic suppression.
2. Three phase I bioequivalence and/or bioavailability studies demonstrated that D/C/F/TAF has a pharmacokinetic profile similar to that of the individual components D/C and F/TAF, administered in combination.
3. At the manufacturer-submitted price of $52.44 per day, D/C/F/TAF is more costly than other triple or quadruple STRs with similar indications that are recommended in treatment guidelines.

Discussion Points

- Recommendations such as the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV issued by the US Department of Health and Human Services generally recommend integrase strand transfer inhibitor–based triple or quadruple STRs as initial regimens for most people with HIV. Clinician expert input indicated that protease inhibitor–based therapies are therefore not considered first-line therapy for most patients with HIV because of the need for pharmacologic boosting and because of several adverse effects in their safety profile (e.g., diarrhea, worsening glucose intolerance, dyslipidemia).
- CDEC noted that there is an unmet need for an STR for patients with past treatment failure and genotypic viral resistance. However, the 800 mg daily dose of darunavir in Symtuza is lower than the 600 mg twice daily dose of darunavir that is recommended for treatment in patients with darunavir-resistant virus. Hence, D/C/F/TAF does not appear to meet this unmet need.
- Long-term bone health and future fracture risk with administration of this drug are unknown, given the available data. The clinical expert expressed concern about the long-term use of TAF in adolescents because of its potential impact on bone development in this population.
- Patients with hepatitis B or hepatitis C coinfection were excluded from the included RCTs. The safety and efficacy of D/C/F/TAF in these patients has not been established.

Background

D/C/F/TAF fixed-dose combination (FDC) has a Health Canada indication for a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with no known mutations associated with resistance to the individual components of D/C/F/TAF. It is a single-tablet FDC that consists of darunavir (D) 800 mg, cobicistat (C) 150 mg, emtricitabine (F) 200 mg, and tenofovir alafenamide (TAF) 10 mg.

Summary of CDEC Considerations

The Committee considered the following information prepared by CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the therapeutic rationale, place in therapy, efficacy, and harms for D/C/F/TAF, as well as a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience in treating patients with HIV infection, and information submitted by patient groups about outcomes and issues important to patients.

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 D/C/F/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.
- Patients with HIV often experience "accelerated aging" and become more susceptible to inflammatory and noninfectious comorbidities; in addition, these patients often experience negative mental health outcomes.
- There remains an unmet need, as some patients are still unable to achieve viral suppression, despite attempts with multiple different treatment regimens.
- Treatment adherence is particularly important with regard to HIV treatment, as nonadherence 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 review included one phase II RCT (GS-US-299-0102, double-blind, noninferiority design, N = 153) and two ongoing phase III RCTs (AMBER, double-blind, noninferiority design, N = 725; EMERALD, open-label, noninferiority design, N = 1,141). In GS-US-299-0102 and AMBER, the efficacy and safety of D/C/F/TAF (800 mg/150 mg/200 mg/10 mg) FDC once daily were compared with co-administration of D 800 mg + C 150 mg + F/TDF combination 200 mg/300 mg once daily, or the co-administration of D/C combination (800 mg/150 mg) with F/TDF combination (200 mg/300 mg) in antiretroviral therapy–naive patients. In EMERALD, patients with virologic suppression who had been treated with a stable antiretroviral therapy consisting of a bPI combined with F/TDF were randomized to switch to D/C/F/TAF FDC once daily or to continue their original regimen of bPI + F/TDF.

Outcomes

The following outcomes were evaluated:

- Virologic success or rebound — percentage of patients with HIV-1 RNA < 50 (success) or ≥ 50 copies/mL (rebound) (FDA-defined snapshot algorithm)
- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms (renal and bone systems).

The primary efficacy end point of GS-US-299 and AMBER was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 24 (GS-US-299-0102) or week 48 (AMBER), using the FDA-defined snapshot algorithm. The primary efficacy end point in EMERALD was the proportion of patients with virologic rebound (HIV-1 RNA ≥ 50 copies/mL, using the FDA-defined snapshot algorithm) through week 48 after the start of treatment.

Efficacy

- In GS-US-299-0102, D/C/F/TAF FDC was noninferior to co-administration of the individual components of D, C, and F/TDF for virologic success in treatment-naive patients at week 24 of the treatment. The difference in proportion was 3.3% (95% confidence interval [CI], –11.4% to 18.1%; *P* = 0.64 [full analysis set]).
- In AMBER, D/C/F/TAF FDC was noninferior to co-administration of D/C and F/TDF for virologic success in treatment-naive patients at week 48 of the treatment. The difference in proportion was 2.7% (95% CI, –1.6% to 7.1%; *P* < 0.0001 [intention-to-treat analysis set]).
- In EMERALD, switching to D/C/F/TAF FDC was noninferior to remaining on treatment with bPI + F/TDF for the proportion of patients with virologic rebound through 48 weeks in patients with virologic suppression. The difference in proportion was 0.4% (95% CI, –1.5% to 2.2%; *P* < 0.001 [intention-to-treat analysis set]).

Harms (Safety and Tolerability)

- In GS-US-299-0102, the risk of treatment-emergent adverse events was similar between D/C/F/TAF FDC (92%) and co-administration of D, C, and F/TDF (94%) in treatment-naive patients. Risk of serious adverse events was 4.9% for patients in the D/C/F/TAF group and 4% in the control group. Adverse events leading to premature study drug discontinuation were reported in 1.9% of patients in the D/C/F/TAF group and 4% in the control group. Diarrhea (21.4%), upper respiratory tract infection (15.5%), fatigue (13.6%), nausea (12.6%), and rash (11.7%) were the most common adverse events reported by patients receiving D/C/F/TAF. Patients in the D/C/F/TAF group showed a better renal safety profile and less decline in bone mineral density than those receiving D, C, and F/TDF.
- Results of AMBER and EMERALD indicated that treatment-emergent adverse effects related D/C/F/TAF FDC occurred in 82% to 86% of participants. No new adverse events were identified beyond those known to be associated with the individual components of D/C/F/TAF.

Cost and Cost-Effectiveness

The manufacturer undertook a cost comparison, which indicated that, at the submitted daily price of $52.44 per tablet, D/C/F/TAF FDC is at parity with its individual components D/C ($23.87 daily) and F/TAF ($28.57 daily), based on publicly available prices.

CDR identified the following issues for consideration:

- The use of D/C/F/TAF FDC may lead to cost savings on the price of a dispensing fee compared with regimens using its individual component medications.
- Patients favour STRs over multi-tablet regimens because of their convenient administration, according to feedback from the clinical expert consulted by CDR.
- Prices for D/C and other comparator STRs vary across CDR-participating drug plans and may lead to variations in potential cost savings, depending on the jurisdiction.
- CDR compared the cost of D/C/F/TAF with the cost of other STRs, based on feedback from the clinical expert consulted by CDR. At the submitted price, D/C/F/TAF is more costly than the publicly available price of other STRs, with the annual cost ranging from $1,614 to $10,869 higher.

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.

June 20, 2018 Meeting

Regrets

None

Conflicts of Interest

None