CDEC FINAL RECOMMENDATION

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE

(Stribild – Gilead Sciences Canada Inc.)

Indication: HIV-1 Infection in Antiretroviral Treatment-Naive Adults

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Stribild be listed as a complete regimen for antiretroviral treatment-naive HIV-1 infected patients with the following clinical criterion:

- Patients in whom efavirenz (EFV) is not indicated.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs), conducted in treatment-naive patients, demonstrated that Stribild was non-inferior to EFV/emtricitabine (FTC)/tenofovir (TDF) (Atripla; Study 102) and ritonavir-boosted atazanavir (ATV/r) plus FTC/TDF (Study 103) for virologic success based on the proportion of patients who achieved a viral load of less than 50 copies/mL at 48 and 96 weeks.

2. Stribild ($45.52 daily) is more expensive than other once-daily fixed-dose combinations – Atripla ($41.40 daily) and rilpivirine/FTC/TDF (Complera; $40.43 daily), but is less costly compared with ATV/r plus FTC/TDF ($50.20 daily), raltegravir plus FTC/TDF ($53.63 daily), and ritonavir-boosted darunavir plus FTC/TDF ($49.18 daily).

Of Note:

1. CDEC noted that the use of EFV may be precluded in treatment-naive patients who have been screened and found to have viral resistance to EFV; patients who started an EFV-containing regimen, but were unable to continue treatment due to adverse effects; and patients with pre-existing comorbidities that, in the opinion of the treating clinician, make EFV a suboptimal treatment choice.

2. At the time of the Common Drug Review (CDR) review, Stribild was listed as an alternative United States Department of Health and Human Services (DHHS) regimen for the initial treatment of HIV-1 infected patients.

Background:
Stribild consists of the standard dual N(t)RTI backbone (FTC 200 mg and TDF 300 mg); elvitegravir 150 mg, an integrase strand inhibitor; and cobicistat 150 mg, an inhibitor of CYP 3A-dependent metabolism that increases the bioavailability of elvitegravir. Cobicistat and elvitegravir are currently only available in Canada as components of Stribild. A single-tablet coformulation, Stribild has a Health Canada indication as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients aged 18 years and older. Stribild is administered orally once daily with food.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of Stribild, a supplementary review of recently available 96-week data, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information
Two patient groups responded to the CDR call for patient input for this review. The patient groups stated the following:

- Outcomes of importance to patients include improved effectiveness and adverse event profiles (including psychiatric side effects) compared with current regimens and improved adherence to treatment (especially for patients in challenging life situations).
- The strict adherence requirements of HIV drug regimens can be challenging for patients and their caregivers. Improved adherence could lead to better health outcomes, fewer subsequent infections, and reduce the development of drug class resistance.

Clinical Trials
The systematic review included two phase 3 non-inferiority RCTs (Study 102 and Study 103) and one phase 2 RCT (Study 104); all of which were multicentre, double-blind, double-dummy, active-controlled trials stratified by HIV-1 RNA load (≤ 100,000 copies/mL or > 100,000 copies/mL). Studies 102 (N = 707) and 103 (N = 715) were 96 weeks in duration and Study 104 (N = 71) was 48 weeks in duration. Study 102 and 104 compared Stribild with Atripla (fixed-dose, coformulated EFV 600 mg/FTC 200 mg/TDF 300 mg) while Study 103 compared Stribild with ATV/r (300 mg/100 mg) plus FTC/TDF (200 mg/300 mg) in treatment-naive adult patients aged 18 years and older.

Patients enrolled in Studies 102 and 103 were predominantly male (approximately 90%) and Caucasian (approximately 70%), with a mean age of 38 years, a mean CD4+ cell count of 378/mcL, and asymptomatic HIV disease (> 80%). Approximately two-thirds of patients had a baseline HIV-1 RNA viral load ≤ 100,000 copies/mL with a mean of 4.8 $\log_{10}$ copies/mL. In all three studies, viral genotyping was required to confirm sensitivity to the antiretroviral therapies used in the trials.

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

- Virologic success – percentage of patients with a viral load < 50 copies/mL at 48 weeks using the United States Food and Drug Administration (FDA)-defined snapshot analysis (primary outcome) and the FDA-defined time to loss of virologic response (TLOVR) algorithm (secondary end point).

- Virologic failure – percentage of patients whose last HIV-1 RNA value was ≥ 50 copies/mL in the week 48 analysis window while on randomized treatment; or who did not have on-treatment HIV-1 RNA data in the window due to study drug discontinuation because of lack of efficacy (or discontinuation due to reasons other than adverse events, death, or lack of efficacy, with a last measured HIV-1 RNA value ≥ 50 copies/mL).
- Reduction of $\log_{10}$ viral load from baseline to week 48.
- Change in CD4+ count from baseline to week 48.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

Non-inferiority of Stribild relative to Atripla (Study 102) and relative to ATV/r plus FTC/TDF (Study 103) was assessed using a margin of 12%.

Results

Efficacy

- In Study 102, there was no statistically significant difference in the proportion of patients who achieved a viral load of < 50 copies/mL at week 48 with Stribild (87.6%) compared with Atripla (84.1%) (risk difference 3.6%; 95% CI: –1.6 to 8.8) in the intention-to-treat (ITT) analysis. Similar results were demonstrated using the per-protocol analysis (risk difference –1.0%; 95% CI: –4.4 to 2.4) and the TLOVR analysis (stratum-weighted difference 2.7%; 95% CI: –2.6 to 8.1). Stribild was non-inferior to Atripla using both ITT and per-protocol analyses.
- In Study 103, there was no statistically significant difference in the proportion of patients who achieved a viral load of < 50 copies/mL at week 48 (snapshot analysis) with Stribild (89.5%) compared with ATV/r plus FTC/TDF (86.8%) (risk difference 3.0%; 95% CI: –1.9 to 7.8) in the ITT analysis. Similar results were demonstrated using the per-protocol analysis (risk difference –0.1%; 95% CI: –2.6 to 2.4) and the TLOVR analysis (stratum-weighted difference 1.6%; 95% CI: –3.6 to 6.8). Stribild was non-inferior to ATV/r plus FTC/TDF using both ITT and per-protocol analyses.
- In both Study 102 and Study 103, the pre-specified subgroup analysis by baseline viral load (i.e., ≤ 100,000 or > 100,000 copies/mL) did not reveal any treatment by baseline viral load interactions, with both subgroups achieving rates of viral load suppression consistent with those of the primary analysis.
- Virologic failure occurred at a similar rate between groups in Study 102 and 103 at week 48: 7.2% of Stribild patients compared with 7.1% of Atripla patients in Study 102; and 5.4% of Stribild patients and 5.4% of ATV/r plus FTC/TDF patients in Study 103.
- The proportion of patients who developed resistance mutations to the study drugs was low in the included trials: Study 102 (2.3% with Stribild and 2.3% with Atripla); and Study 103 (1.4% with Stribild and 0% with ATV/r plus FTC/TDF).
- Results for other efficacy outcomes, such as mean reduction in viral load and mean change in CD4 counts, were similar between Stribild and comparators.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was greater with Stribild (11.8%) compared with Atripla (6.8%) in Study 102, and similar between Stribild and ATV/r plus FTC/TDF in Studies 103 (7.4% versus 8.7%) and 104 (4.2% versus 4.3%). Three deaths were reported in Study 102 (one in the Stribild group), three in Study 103 (all three in the ATV/r plus FTC/TDF group), and none in Study 104.

- The majority of patients in each trial experienced at least one adverse event whether randomized to Stribild or a comparator (Study 102: 94.0% versus 94.9%; Study 103: 91.5% versus 93.8%; Study 104: 91.7% versus 91.3%). Diarrhea, nausea, and headache were the most commonly reported adverse events reported in the Stribild groups. Psychiatric adverse events were reported in a lower proportion of patients in the Stribild group compared with the Atripla group in Study 102 (33.9% versus 46.3%). These psychiatric adverse effects included abnormal dreams, anxiety, and depression.
- Withdrawals due to adverse events were reported as follows: Study 102 (3.7% with Stribild and 5.1% with Atripla); Study 103 (3.7% with Stribild and 5.1% with ATV/r plus FTC/TDF); and Study 104 (0% with Stribild and 4.3% with Atripla).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing Stribild with an evenly weighted basket of the DHHS preferred regimens. The clinical evidence used to support the assumption of similar clinical efficacy and safety was based on head-to-head trials of Stribild compared with Atripla and ATV/r plus FTC/TDF, and a naive indirect comparison with other preferred regimens based on the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* developed by the DHHS. The manufacturer's analysis did not include Complera, a fixed-dose combination drug taken once daily. However, the clinical expert consulted by the CDR indicated that Complera is a relevant comparator; therefore, it was included in the CDR review.

Stribild ($45.52 daily) is more expensive than other once-daily fixed-dose combinations – Atripla ($41.40 daily) and Complera ($40.43 daily), but it is less costly compared with ATV/r plus FTC/TDF ($50.20 daily), raltegravir plus FTC/TDF ($53.63 daily), and ritonavir-boosted darunavir plus FTC/TDF ($49.18 daily).

Other Discussion Points:

CDEC noted the following:

- Approximately 90% of patients in the included RCTs (Studies 102 and 103) were male; therefore, there is limited data regarding the safety and efficacy of Stribild in the treatment of women. The FDA has recommended that RCTs be conducted to assess the safety and efficacy of Stribild in women.
- The Health Canada approved indication for Stribild specifies antiretroviral treatment-naive patients and the RCTs included in the CDR submission were limited to these patients. There was no evidence in the CDR submission regarding the safety and efficacy of Stribild in treatment-experienced patients.
- At the time of the CDR review, Stribild was not listed as a DHHS preferred regimen for the treatment of HIV-1 infected patients.
- There is uncertainty regarding the long-term renal toxicity of Stribild.
- Resistance data were insufficient to draw conclusions regarding any differences between treatments.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

April 17, 2013 Meeting

Regrets:
None

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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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