



CDEC FINAL RECOMMENDATION

RILPIVIRINE/EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE (Complera – Gilead Sciences Inc.)

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

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that Complera be listed for the treatment of human immunodeficiency virus type 1 (HIV-1) in antiretroviral treatment-naive patients, or to replace the three components given as dual or triple therapy for patients stabilized on appropriate doses.

Reasons for the Recommendation:

1. In one double-blind randomized controlled trial (RCT) in treatment-naive patients with HIV-1 infection, rilpivirine given with emtricitabine/tenofovir was non-inferior to the combination of efavirenz plus emtricitabine/tenofovir, based on the percentage of patients achieving undetectable viral loads (< 50 copies/mL) at 48 weeks.
2. At the submitted price, the daily cost of Complera (\$39.61) is equal to the sum of the costs of the individual components (rilpivirine, emtricitabine/tenofovir), similar to Atripla (efavirenz/emtricitabine/tenofovir; \$40.12), and lower than other treatments considered to be preferred, based on the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* developed by the United States Department of Health and Human Services (\$47.70 to \$52.81).

Background:

Complera has a Health Canada indication for use alone as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naive adults. Complera is a fixed-dose combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI; emtricitabine and tenofovir disoproxil fumarate) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI; rilpivirine). It is available as an oral tablet containing a fixed-dose combination of rilpivirine 25 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg; the dose approved by Health Canada is one tablet, once daily.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of the combination of rilpivirine, emtricitabine,

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and tenofovir disoproxil fumarate, and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

The systematic review included one double-blind, non-inferiority RCT of treatment-naive patients with HIV-1 infection. ECHO (N = 690) randomized patients to either rilpivirine (25 mg daily) or efavirenz (600 mg daily); randomization was stratified by viral load ($\leq 100,000$ copies/mL, $>100,000$ to $\leq 500,000$ copies/mL, or $>500,000$ copies/mL). All patients received emtricitabine (200 mg daily) plus tenofovir disoproxil fumarate (300 mg daily). Treatment duration was 96 weeks.

ECHO enrolled adult patients with an HIV-1 viral load $\geq 5,000$ copies/mL, who were treatment naive, with virus susceptible to emtricitabine and tenofovir disoproxil fumarate at screening, and who had no NNRTI resistance-associated mutations at screening. Pregnant women were excluded from the trial.

The frequency of study withdrawal was approximately 15%, and was similar across treatment groups. However, reasons for withdrawal differed between treatments: rilpivirine patients primarily withdrew due to virologic failure, whereas efavirenz patients primarily withdrew due to adverse events.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, quality of life, percentage of patients achieving an undetectable viral load, virologic failure, viral resistance, serious adverse events, and adverse events.

The primary outcome was the percentage of patients achieving an undetectable viral load (< 50 copies/mL) at week 48. The non-inferiority margin for the primary outcome was set at 12%. Patients who prematurely discontinued the trial or had a loss of response (≥ 50 copies/mL at two consecutive visits) were considered not to have achieved an undetectable viral load at all time points after discontinuation or loss of response.

Quality of life was assessed using the 36-Item Short Form Health Survey, version 2 (SF-36v2).

Results

Efficacy or Effectiveness

- There were no deaths in the ECHO trial at 48 weeks; by 96 weeks, there were three deaths in the efavirenz group but none in the rilpivirine group.
- At 48 weeks, the percentage of patients achieving undetectable viral load was approximately equal for rilpivirine and efavirenz (82.9% versus 82.8%, respectively). The non-inferiority criterion was met for both the intention to treat and per-protocol populations. Similar results were reported at 96 weeks.
- The percentage of patients experiencing virologic failure was statistically significantly greater for patients treated with rilpivirine than for those treated with efavirenz at both 48 and 96 weeks; 11.0% versus 4.4%, and 13.0% versus 4.7%, respectively. Between-

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treatment differences in virologic failure were greatest in subgroups of patients whose viral loads were > 100,000 copies/mL.

- Patients experiencing virologic failure on rilpivirine and who were resistant to rilpivirine at virologic failure demonstrated high rates of cross-resistance to other NNRTIs including efavirenz (82%), etravirine (91%), and nevirapine (46%), based on 48-week data. In contrast, 0% of patients experiencing virologic failure on efavirenz, and who demonstrated resistance to efavirenz, experienced cross-resistance to rilpivirine or etravirine, although there was 100% cross-resistance to nevirapine.
- Changes in quality of life, based on SF-36v2 scores, were not statistically significantly different between rilpivirine and efavirenz at 48 weeks.

Harms (Safety and Tolerability)

- The incidence of serious adverse events and total adverse events was similar between rilpivirine and efavirenz.
- The percentage of patients reporting rash was numerically lower for rilpivirine than for efavirenz (7% versus 12%), as was the percentage of patients experiencing psychiatric effects (23% versus 33%).
- The percentage of patients experiencing nervous system disorders was numerically lower for rilpivirine than for efavirenz (27% versus 43%), primarily due to a lower incidence of dizziness for rilpivirine.

Cost and Cost-Effectiveness

The manufacturer submitted a cost minimization analysis comparing Complera with Atripla (efavirenz/emtricitabine/tenofovir) in treatment-naïve adults with HIV-1. This approach was supported by the ECHO trial. The daily cost of Complera (\$39.61) is equal to the sum of the costs of the individual components (rilpivirine, emtricitabine/tenofovir), similar to Atripla (\$40.12), and lower than other treatments considered preferred, based on the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* developed by the United States Department of Health and Human Services (\$47.70 to \$52.81).

Patient Input Information:

No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:

- The Committee noted that the percentage of patients experiencing virologic failure was statistically significantly higher for rilpivirine than for efavirenz in the ECHO trial. This finding appeared to be driven by patients with viral loads > 100,000 copies/mL. Further, the Committee noted the association between virologic failure with rilpivirine and the development of cross-resistance to other antiretrovirals. However, the Committee considered that patients with HIV-1 infection are under the care of physicians experienced in the management of antiretroviral therapy.
- The Committee noted that in a phase 1 bioequivalence study, Complera was shown to be bioequivalent to its three individual component drugs administered concurrently.
- The Committee noted that ongoing trials include a phase 2b trial switching virologically suppressed patients on efavirenz/emtricitabine/tenofovir to rilpivirine/emtricitabine/tenofovir, and a phase 3 safety and efficacy trial switching patients receiving a protease-inhibitor based regimen to rilpivirine/emtricitabine/tenofovir.

- The Committee noted that the cost of comparators to Complera may decrease in 2012, with a number of patents for comparators expected to expire.

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.

March 21, 2012 Meeting**Regrets:**

None

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. 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*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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