



CDEC FINAL RECOMMENDATION

RILPIVIRINE

(Edurant – Janssen Inc.)

Indication: HIV in Treatment-Naive Adult Patients

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that rilpivirine be listed, when used in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-naive patients.

Reasons for the Recommendation:

1. In two double-blind randomized controlled trials (RCTs), when used in combination with two other antiretroviral agents in treatment-naive patients with HIV-1 infection, rilpivirine was non-inferior to efavirenz, 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 rilpivirine plus tenofovir/emtricitabine (\$39.61) is similar to efavirenz/tenofovir/emtricitabine (Atripla; \$40.12) and lower than other treatments preferred by the United States Department of Health and Human Services (\$47.70 to \$52.81).

Background:

Rilpivirine, when used in combination with other antiretroviral agents, has a Health Canada indication for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients. Rilpivirine is a non-nucleoside reverse-transcriptase inhibitor (NNRTI). It is available as 25 mg oral tablets and the Health Canada–recommended dose is 25 mg daily, which must be taken with a meal to obtain optimal absorption.

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 rilpivirine, a critique of the manufacturer's pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues important to patients.

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Clinical Trials

The systematic review included two double-blind non-inferiority RCTs of patients with HIV-1 infection. ECHO (N = 690) and THRIVE (N = 678) both randomized patients to either rilpivirine (25 mg daily) or efavirenz (600 mg daily); randomization in both trials was stratified by viral load ($\leq 100,000$ copies/mL; $> 100,000$ copies/mL to $\leq 500,000$ copies/mL; or $> 500,000$ copies/mL). The two trials differed with respect to the concomitant background regimen used. In ECHO, all patients received tenofovir disoproxil fumarate (300 mg daily) plus emtricitabine (200 mg daily). In THRIVE, patients received one of the following three investigator-selected background regimens: abacavir (600 mg daily) plus lamivudine (300 mg daily); zidovudine (300 mg daily) plus lamivudine (300 mg daily); or tenofovir disoproxil fumarate (300 mg daily) plus emtricitabine (200 mg daily). Treatment duration in both trials was 96 weeks.

Both ECHO and THRIVE enrolled adult patients with an HIV-1 viral load $\geq 5,000$ copies/mL, who were treatment naive, susceptible to their background regimen at screening, and had no NNRTI resistance-associated mutations at screening. Pregnant women were excluded from both trials.

The frequency of study withdrawal was approximately 15% in both trials, and was similar across treatment groups in both trials. 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 in the two trials 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 times after discontinuation or loss of response.

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

Results

Efficacy or Effectiveness

- There were no deaths in the ECHO trial. In THRIVE, one death occurred in the rilpivirine treatment group, compared with three deaths for efavirenz.
- In ECHO, at 48 weeks, the percentage of patients achieving undetectable viral load was approximately equal for rilpivirine and efavirenz (82.9% versus 82.8%, respectively). In THRIVE, at 48 weeks, 85.6% of rilpivirine-treated patients achieved an undetectable viral load compared with 81.7% of efavirenz-treated patients. The non-inferiority criterion was met for both the intention to treat and per-protocol populations in both trials. Similar results were reported at 96 weeks.

- In one trial (ECHO), the percentage of patients experiencing virologic failure was statistically significantly greater for patients treated with rilpivirine than with efavirenz at both 48 and 96 weeks: 11.0% versus 4.4%, and 13.0% versus 4.7%, respectively. Between-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 also resistant to rilpivirine at virologic failure demonstrated high rates of cross-resistance to other NNRTIs, including efavirenz (82% to 100%), etravirine (89% to 91%), and nevirapine (44% to 80%). In contrast, 0% of patients experiencing virologic failure on efavirenz and who also demonstrated resistance to efavirenz, demonstrated resistance to rilpivirine or etravirine; although there was 100% cross-resistance to nevirapine among efavirenz-resistant patients.
- Changes in quality of life, based on SF36v2 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 efavirenz in both ECHO (7% versus 12%) and THRIVE (4% versus 14%). The percentage of patients experiencing psychiatric effects was numerically lower for rilpivirine than efavirenz in ECHO (23% versus 33%), but was the same in THRIVE (25% for both treatments).
- The percentage of patients experiencing nervous system disorders was numerically lower for rilpivirine than efavirenz in both ECHO (27% versus 43%) and THRIVE (35% versus 51%), primarily due to a lower incidence of dizziness for rilpivirine.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing rilpivirine with efavirenz for antiretroviral treatment-naive adult patients, based on the ECHO and THRIVE RCTs. These trials were conducted in treatment-naive adults and reported the non-inferiority of rilpivirine compared with efavirenz for the proportion of virologic responders at 48 weeks. All costs between treatments were assumed to be equivalent, including the cost of backbone regimens (e.g., nucleoside reverse transcriptase inhibitors [NRTIs]).

The manufacturer's cost-minimization analysis was limited by lack of consideration for the patent expiry, expected in the near future, of comparators, including efavirenz/tenofovir/emtricitabine (Atripla) and efavirenz (Sustiva). The model also did not account for treatment-emergent NNRTI and NRTI resistance with rilpivirine compared with efavirenz, and the potential for a virus that is more difficult and costly to treat.

The daily cost of rilpivirine plus tenofovir/emtricitabine (\$39.61) is similar to efavirenz/tenofovir/emtricitabine (Atripla; \$40.12) and lower than other treatments preferred by the US Department of Health and Human Services (\$47.70 to \$52.81).

Patient Input Information:

The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input:

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- Patients emphasized the need for additional treatment options, with fewer side effects than current treatments. Specifically, psychiatric adverse effects and increased risk of liver problems in women were mentioned as reasons that patients were reluctant to use efavirenz and nevirapine, respectively.
- The once-daily dosing of rilpivirine, combined with the small pill size, is seen as an advantage, particularly for treatment-naive patients who are unused to complex medication schedules.

Other Discussion Points:

- The Committee noted that the percentage of patients experiencing virologic failure was statistically significantly higher for rilpivirine than for efavirenz in ECHO, and that 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 recognized patient input that emphasized the need for effective treatments with improved tolerability.
- The Committee noted that patents for Atripla (efavirenz/tenofovir/emtricitabine) and Sustiva (efavirenz) are expected to expire in the near future.

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

January 18, 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*.

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