



COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

RALTEGRAVIR

(Isentress – Merck Frosst Canada Ltd.)

New Indication: HIV-1, Treatment-Naive

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that raltegravir not be listed at the submitted price.

Reason for the Recommendation:

In one double-blind randomized controlled trial in treatment-naive patients, the proportion of patients with HIV-1 RNA < 50 copies/mL, serious adverse events, or withdrawals due to adverse events was similar for raltegravir compared with efavirenz when used in combination with emtricitabine and tenofovir. At the [REDACTED] price submitted, raltegravir costs substantially more than efavirenz. Confidential information was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Of Note:

1. Based on a review of the clinical evidence, the Committee felt that a reduced price could improve raltegravir's cost-effectiveness in treatment-naive patients and, thereby, increase the likelihood of a recommendation to "list" or "list with criteria."
2. The Committee noted that although in clinical trials the efavirenz groups had more patients reporting dizziness, diarrhea, and rash compared with the raltegravir group, there is substantial clinical experience in managing these adverse effects.

Background:

Raltegravir has a Health Canada indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. The focus of this recommendation is the use of raltegravir in treatment-naive adults with HIV-1. Raltegravir is an integrase inhibitor that acts by inhibiting the catalytic activity of HIV integrase, an HIV-encoded enzyme that is required for viral replication. The recommended dose of raltegravir is 400 mg taken orally twice daily. It is available as a 400 mg tablet.

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Submission History:

Raltegravir was previously reviewed by CEDAC for its use in treatment-experienced HIV-1 patients and received a recommendation to list for the treatment of HIV infection in patients who are antiretroviral-experienced and have virologic failure due to resistance to at least one agent from each of the three major classes of antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors (see Notice of CEDAC Final Recommendation, May 14, 2008).

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind (DB) randomized controlled trials (RCTs) of raltegravir in treatment-naive patients with HIV-1 infection and a critique of the manufacturer's pharmaco-economic evaluation. The manufacturer submitted a [REDACTED] price for raltegravir.

Clinical Trials

The CDR systematic review included two DB RCTs comparing the effect of raltegravir to that of efavirenz, given in combination with other antiretroviral therapy in treatment-naive patients with HIV infection. In both RCTs, treatment-naive patients with HIV were included if they had baseline viral loads of > 5,000 copies/mL and CD4 cell counts above 100 cells/ μ L.

- STARTMRK (N = 563) was designed to evaluate the non-inferiority of raltegravir 400 mg twice daily to efavirenz 600 mg daily. All patients also received the fixed-dose combination of 200 mg emtricitabine and 300 mg tenofovir daily.
- Study 004 (N = 201) was a dose-ranging study that compared four different doses of raltegravir with efavirenz. The CDR review focused only on the Health Canada-approved dose of raltegravir of 400 mg twice daily (N = 79). All patients also received 300 mg of lamivudine and 300 mg of tenofovir daily.

In both studies, after 48 weeks, patients were eligible to participate in DB, controlled, extension phases, which are ongoing up to 240 weeks. Data up to 96 weeks for STARTMRK and up to 48 weeks for Study 004 were considered in the CDR review.

Patient withdrawals ranged from 13% to 18% and were similar across studies and treatment groups.

Outcomes

The primary outcome of STARTMRK was the proportion of patients with HIV-1 RNA < 50 copies/mL at 48 weeks and in Study 004 it was the proportion of patients with HIV-1 RNA < 400 copies/mL at 48 weeks.

Other outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in CD4 cell counts, emergence of resistance, and changes in lipid profiles.

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Quality of life was not measured in either study. Neither study was designed to measure HIV-related morbidity and mortality.

Results

Efficacy or Effectiveness

- In STARTMRK, there was no statistically significant difference in the proportion of patients achieving HIV-1 RNA < 50 copies/mL at 48 weeks between raltegravir and efavirenz (86% versus 82%, relative risk 1.05, 95% confidence interval 0.98 to 1.13, P = 0.18). This was the primary outcome of STARTMRK and the non-inferiority criteria were met (non-inferiority margin 12%). The results from Study 004 supported this finding. Results were similar in both studies at 96 weeks.
- The proportion of patients achieving HIV-1 RNA < 400 copies/mL at 48 weeks was similar between raltegravir and efavirenz in both studies.
- Changes in CD4 cell counts were greater for raltegravir compared with efavirenz at 48 weeks, but similar for raltegravir and efavirenz at 96 weeks in STARTMRK. There was no difference between the two treatments at 48 weeks or 96 weeks for Study 004.
- The proportion of patients experiencing virologic failure and the time to virologic failure was similar between raltegravir and efavirenz regimens. Virologic failure was defined as either a non-response (a viral load above 50 copies/mL in STARTMRK or above 400 copies/mL in Study 004 at 24 weeks or early discontinuation) or as rebound. Rebound was defined as an initial response followed by two consecutive viral loads, taken at least one week apart, above the limit of detection.
- There were too few events at 96 weeks to assess the relative effects of raltegravir and efavirenz on HIV-related morbidity or mortality.

Harms (Safety and Tolerability)

- Serious adverse events and withdrawals due to adverse events were similar between raltegravir and efavirenz groups in both studies. None of the withdrawals due to adverse events were due to hepatic impairment.
- In STARTMRK, statistically significantly fewer raltegravir patients had an adverse event compared with efavirenz patients at 48 weeks (90% versus 97%), but no differences were observed at 96 weeks. Statistically significantly fewer raltegravir patients compared with efavirenz patients reported dizziness (8% versus 37%), diarrhea (17% versus 25%), and rash (6% versus 12%).
- In STARTMRK, raltegravir had a statistically significantly smaller effect on cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides compared with efavirenz. In Study 004, similar results were observed for cholesterol and triglycerides. In both studies, some patients were receiving concomitant lipid-lowering agents.
- Resistance testing was only conducted on patients who experienced virologic failure in STARTMRK. For the 12 raltegravir patients who were tested, both of the two nonresponders and two of the 10 rebounders had integrase mutations.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing raltegravir plus tenofovir/emtricitabine with efavirenz plus tenofovir/emtricitabine in treatment-naive patients with HIV-1 during a 50-year time horizon. The manufacturer considered treatment sequences in their analysis. The manufacturer reported that when comparing raltegravir followed by a protease

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inhibitor with efavirenz followed by a protease inhibitor, raltegravir was associated with a cost per quality-adjusted life-year (QALY) of \$93,092. A number of limitations were identified by CDR that increased the incremental cost-effectiveness ratio, such as the results being highly sensitive to the choice of second-line therapy and the model assumption that raltegravir was superior to efavirenz; while the STARTMRK trial showed raltegravir was non-inferior to efavirenz. When similar effects of raltegravir and efavirenz were assumed, the incremental cost-effectiveness ratios increased to more than \$146,000 per QALY.

At the [REDACTED] price submitted, the daily cost of raltegravir (400 mg twice daily) is \$ [REDACTED], which is substantially more than the daily cost of efavirenz (\$14.08; 600 mg daily) and [REDACTED] the daily cost of atazanavir plus ritonavir (\$22.18; 300 mg and 100 mg daily) and darunavir plus ritonavir (\$22.42; 800 mg and 100 mg daily). Tenofovir / emtricitabine (200 mg / 300 mg daily) costs \$25.05 daily. Confidential information was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Other Discussion Points:

- The Committee discussed the potential listing of raltegravir for use in treatment-naive patients with virologic failure due to resistance to at least one agent from each of the three major classes of antiretroviral agents (nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors), but the Committee considered that there would be very few treatment-naive patients meeting these criteria and that the included RCTs did not specifically evaluate this patient population.
- The Committee discussed that there are a number of other treatment options for treatment-naive patients for which the long-term harms profiles are better known than raltegravir.
- The Committee discussed that there is insufficient evidence to determine the relative potential for the development of HIV-1 resistance to raltegravir over the long-term compared with other antiretroviral drugs.
- The Committee noted that the clinical significance of changes in lipid profiles in patients receiving efavirenz has not yet been demonstrated; therefore, the relevance of the improved lipid profile of raltegravir compared with efavirenz is uncertain.
- The Committee discussed that NNRTIs have an increased risk for drug-drug interactions. In the STARTMRK trial, there was no difference between efavirenz and raltegravir with respect to patients withdrawing as a result of drug-drug interactions.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

Dr. Doug Coyle and Dr. Alan Forster.

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

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About this Document:

CEDAC 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 CEDAC made its recommendation.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC 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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