Summary of Canadian Expert Advisory Committee (CEDAC) Discussion

Raltegravir (Isentress™ — Merck Frosst Canada Ltd.)

Indication – HIV Infection

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating

Dr. Braden Manns (Chair), Dr. Anne Holbrook (Vice-Chair),
Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Malcolm Man-Son-Hing, Dr. Laurie Mallery, Ms. Nancy McColl, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Robert Peterson, Dr. Dale Quest, Dr. Kelly Zarnke.

Regrets

Dr. Michael Evans.

Conflicts of Interest

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

Description

Raltegravir is approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. It has received a Notice of Compliance with Conditions (NOC/c) from Health Canada, pending results of studies to confirm the clinical benefit. Raltegravir is the first of a new class of antiretroviral agents called integrase inhibitors. The drug inhibits integrase, the enzyme that allows insertion of HIV DNA into the host genome during the early phase of infection, thus preventing HIV replication.

Discussion of Clinical and Pharmacoeconomic Reviews

CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR, and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain language versions) are available in the CDR Drug Database on the CADTH web site (www.cadth.ca).

A presentation by CEDAC members, and the discussion that ensued, addressed the following points:

Therapeutic Rationale and Need

At the end of 2005, Health Canada estimated that 58,000 people were living with HIV in Canada. HIV incidence was estimated at 2,300 to 4,500 new HIV cases in 2005, compared with

2,100 to 4,000 incident cases in 2002. Effective management of HIV infection requires lifelong suppressive therapy. While highly active antiretroviral therapy (HAART) has modified the course of the disease, the treatment of HIV patients who are infected with resistant strains, either de novo or by acquisition, is challenging.

Clinical Trials

Three randomized double-blind placebo-controlled trials evaluated treatment-experienced HIV patients with documented resistance to at least one agent from each of the three major antiretroviral classes. Raltegravir 400 mg twice daily or placebo was added to optimized background therapy (OBT). BENCHMRK-1 and BENCHMRK-2 were two identically designed large multicentre trials (total n=699) and the pooled results from these trials were evaluated. These patients had baseline HIV ribonucleic acid (RNA) >1,000 copies/mL and had been on stable antiretroviral therapy (ART) for two or more months. Follow-up was at 16 and 24 weeks, with some preliminary data from 48 weeks. An open-label option was then possible for up to 96 weeks; however, this data was not available at the time of the review. Protocol 005 was a dose-ranging study (n=45 per treatment arm) and only the arm using the approved dose of raltegravir, 400 mg twice daily, was evaluated. Follow-up was at 16 and 24 weeks, with an open-label option after week 24 (and week 16 for those with virologic failure). CEDAC focused its discussion on the BENCHMRK studies.

Comparators

Eligible studies for review included optimized background therapy (OBT) plus raltegravir compared to OBT with or without placebo. OBT was defined as multiple ART from at least two classes, but preferentially including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and nucleoside or nucleotide reverse transcriptase inhibitors. No studies compared raltegravir with another active ART as add-on therapy to OBT.

The OBT arms in the BENCHMRK studies included enfuvirtide in about 40% of patients, darunavir in about 40% of patients, and tipranavir in about 20% of patients in each arm. Use of these newer agents is indicative of the level of baseline resistance in the patients' HIV isolates. Protocol 005 compared raltegravir with placebo, each added to OBT. About one-third of the subjects received enfuvirtide as part of their baseline therapy.

The addition of raltegravir or placebo to OBT does not necessarily reflect clinical practice as the addition of an agent such as raltegravir would likely replace an agent that is not effective. However, it would not be ethical to remove therapy in this fashion during a clinical trial, and this trial design does assess antiretroviral activity.

Outcomes

All studies included outcomes of HIV RNA <400 copies/mL and <50 copies/mL. The use of the outcome HIV RNA <400 copies/mL was the previous standard of practice and is useful for comparison with older studies; however, maximal virologic suppression is currently defined as HIV RNA <50 copies/mL. The mean change in HIV RNA, CD4 count, as well as adverse events, development of resistance, and death and progression to AIDS were also reported.

While HIV RNA (viral load) and CD4 count are surrogate markers, they are standard outcome measures for the evaluation of antiretroviral therapy. Failure to achieve viral suppression is clearly associated with more rapid development of antiretroviral resistance and progression to

clinical failure. The CD4 count correlates inversely with the risk for acquisition of AIDS-defining illnesses.

Effectiveness

In all three studies, virologic suppression was greater with raltegravir versus placebo:

- The number needed to treat (NNT) to achieve HIV RNA <400 copies/mL ranged from 2 to 3 at weeks 16, 24, and 48.
- The NNT to achieve HIV RNA <50 copies/mL ranged from 2 to 4 at weeks 16, 24, and 48.

The improvement in baseline viral RNA and CD4 count was significantly greater in the raltegravir arms versus placebo in all three studies at week 16, 24, and 48. Health resource utilization (emergency room visits, physician visits, and hospitalization) was not reported.

Safety and Tolerability (harms)

There were no differences in serious adverse events, all adverse events, or withdrawals due to adverse events. There was no difference in deaths and AIDS-defining illnesses, but the studies were not powered to assess this difference. Resistance secondary to integrase gene mutations developed in most patients who experienced virologic failure while on raltegravir.

There was an initial observation of excess malignancies with raltegravir versus placebo in BENCHMRK; however, when the evaluation was adjusted for time at risk, statistical significance was not achieved. Additionally, identification of malignancies was found to be early (likely present before initiation of therapy), and the rate of cancer did not increase over time. Further long-term studies are required to assess this risk.

Cost and Pharmacoeconomic Evaluation

The primary pharmacoeconomic evaluation submitted by the manufacturer (raltegravir as add-on therapy) did not address the most likely use of raltegravir in clinical practice, and was thus considered not clinically relevant. A secondary analysis in which raltegravir was substituted for another agent reported an incremental cost-effectiveness ratio of $6,443 per quality-adjusted life year. This was considered a more realistic estimate. Based solely on drug acquisition cost per day, raltegravir is priced below some of the recently introduced agents indicated for treatment-experienced patients (enfuvirtide, darunavir, tipranavir).

Other Discussion Points

- Raltegravir has been granted a NOC/c. Drug plans may seek further advice once the results from studies addressing the clinical benefit are available.
- The frequency of resistance development with prolonged use (beyond 48 weeks) is unknown.

CEDAC Recommendation

CEDAC recommended that raltegravir be listed for the treatment of HIV infections 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/tide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.

Reasons for the Recommendation

- Raltegravir has been shown to improve virologic and immunologic outcomes in patients who have experienced virologic failure with other antiretroviral therapy.
- Raltegravir is similar or lower in cost compared with other antiretroviral agents currently listed by drug plans for treatment of patients who had experienced virologic failure with other antiretroviral therapy.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.