CEDAC FINAL RECOMMENDATION

MARAVIROC
(Celsentri – ViiV Healthcare ULC)
New Indication: HIV-1, Treatment Naive (Adult)

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that maraviroc not be listed for patients with human immunodeficiency virus type 1 (HIV-1) who are treatment naive.

Reason for the Recommendation:
The one double-blind randomized controlled trial (RCT) in HIV-1 patients who were treatment naive failed to meet one of its co-primary end points based on the preplanned analysis. That is, non-inferiority of maraviroc compared with efavirenz was not demonstrated based on the proportion of patients achieving a viral load of < 50 copies/mL at 48 weeks. In addition, non-response due to virologic failure or viral rebound occurred statistically significantly more frequently in the maraviroc treatment group compared with efavirenz at 96 weeks.

Background:
Maraviroc, when used in combination with other antiretroviral agents, has a Health Canada indication for the treatment of adults infected with chemokine receptor 5 (CCR5)-tropic HIV-1. Maraviroc is a CCR5 antagonist. It is available as 150 mg and 300 mg oral tablets. The Health Canada-approved dose is 300 mg twice daily, but adjustments are recommended (from 150 mg to 600 mg twice daily) based on the patient's concomitant medications.

Submission History:
Maraviroc was previously submitted to the Common Drug Review (CDR) in November 2007, but the submission was withdrawn prior to CEDAC deliberations. Following a resubmission, maraviroc was reviewed for the treatment of HIV-1 in treatment-experienced adults and received a recommendation to list with criteria (see Notice of CEDAC Final Recommendation, November 12, 2008).

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the CDR: a systematic review of double-blind RCTs of maraviroc and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for maraviroc. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

The systematic review included one double-blind RCT of treatment-naive patients with CCR5-tropic HIV-1. The MERIT study was a 96-week study designed to test the non-inferiority of maraviroc to efavirenz, both added on to a background regimen of lamivudine plus zidovudine. The MERIT study was originally planned to include two maraviroc treatment groups (300 mg daily, and 300 mg twice daily) and an efavirenz 600 mg daily group. However, randomization to maraviroc 300 mg daily was halted after 177 patients had been randomized to this group because an interim analysis revealed that the maraviroc 300 mg daily group failed to meet the criteria for non-inferiority. The study was originally planned for a sample size of 1,071, but the decision to halt the maraviroc 300 mg daily group early left the total number of patients randomized at 740, of which 721 were treated.

Patients enrolled in the MERIT study were to be those with HIV-1 who were treatment naive (no more than 14 days of therapy with antiretroviral agents) and who had a viral load of > 2000 copies/mL with CCR5-tropic virus only detected, using the original Trofile assay. Subsequently, the manufacturer performed two post hoc reanalyses of the MERIT study data based on an enhanced sensitivity Trofile assay (ESTA) and the V3 loop genotype test (GTT); these post hoc subgroup analyses excluded 14% and 10%, respectively, of patients used in the original Trofile assay analysis. The V3 loop GTT is currently the standard in Canada for determining HIV-1 tropism.

The frequency of study withdrawal was high (approximately 35%), which was similar for maraviroc and efavirenz. However, reasons for withdrawal differed between treatments: maraviroc patients primarily withdrew due to lack of efficacy, 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, viral load, CD4 counts, proportion of patients with treatment failure, study withdrawal, serious adverse events, and adverse events.

The co-primary outcomes in the MERIT study were the percentage of patients achieving a viral load of less than 400 copies/mL and less than 50 copies/mL at week 48. For each of the co-primary outcomes, the non-inferiority margin was 10%, such that if the lower bound of the confidence interval (CI) for the comparison of maraviroc to efavirenz was above –10%, then non-inferiority of maraviroc to efavirenz would be concluded.

The Committee noted the lack of quality of life data in the reviewed trial.

Results

Efficacy or Effectiveness

- There were five deaths in MERIT, two in the maraviroc group, and three in the efavirenz group, none of which were due to HIV-1.

- At week 48, the intention-to-treat population demonstrated that fewer maraviroc-treated patients achieved an undetectable viral load (< 50 copies/mL) compared with efavirenz, using the original Trofile analysis (65% versus 69%), and non-inferiority of maraviroc was not demonstrated (lower 95% CI boundary of –10.9%). In both the ESTA and V3 loop GTT reanalysis, the non-inferiority of maraviroc was demonstrated in the intention-to-treat populations: lower 95% CI boundaries of –7.4% and –9.2%, respectively. Per-protocol results were consistent with the intention-to-treat results for the original and ESTA analyses; per-protocol results were not provided for the V3 loop GTT analysis.
- At week 48, maraviroc met the criteria for non-inferiority (based on a viral load of < 400 copies/mL) for the intention-to-treat population, in all of the original, ESTA, and V3 loop GTT analyses. However, for the per-protocol population, maraviroc met the criteria for non-inferiority in the ESTA but not the original analysis; per-protocol results were not provided for the V3 loop GTT analysis.
- At 96 weeks, there were statistically significantly more maraviroc patients who were non-responders due to virologic failure or viral rebound compared with efavirenz, in both the original and ESTA analyses; statistical results for this outcome were not provided for the V3 loop GTT analysis.
- CD4 counts increased to a greater extent in maraviroc-treated compared with efavirenz-treated patients, and this difference was statistically significant at both 48 weeks and 96 weeks; mean differences (MD) (95% CI): 26 (7 to 46) and 35 (13 to 58), respectively, in the original analysis. Results were similar in the ESTA analysis.

Harms (Safety and Tolerability)

- The incidence of serious adverse events and total adverse events was similar between maraviroc and efavirenz.
- The proportion of patients withdrawing due to an adverse event was lower for maraviroc (6%) compared with efavirenz (16%). The most common reason for discontinuation due to an adverse event was an increase in liver enzymes, for both maraviroc (7 patients) and efavirenz (11 patients).
- The overall incidence of infection did not differ between maraviroc and efavirenz treatment groups in the MERIT study. There was no indication of an increased incidence of malignancy or elevated liver enzymes with maraviroc compared with efavirenz.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing maraviroc with antiretrovirals (efavirenz, atazanavir, darunavir, lopinavir/ritonavir, and raltegravir) for treatment-naive patients with CCR5-positive HIV-1 in Canada. The clinical evidence to support similar clinical efficacy and harms (the basis for a cost-minimization analysis) was a post hoc subgroup analysis of the MERIT study (versus efavirenz) and a network meta-analysis (versus other antiretrovirals). In calculating the cost of treatment, the manufacturer assumed different nucleoside analogue reverse-transcriptase inhibitor (NRTI) background therapies: lamivudine/zidovudine for maraviroc, and tenofovir/emtricitabine for other antiretroviral comparators. At the confidential submitted price for maraviroc, the manufacturer estimated that maraviroc costs more per month than efavirenz and is cost saving compared with other antiretroviral treatments. [The manufacturer requested that details from the economic evaluation be removed from the preceding sentence.]

A number of limitations with the manufacturer's economic analysis were noted. The key limitation was the lack of data to support similar clinical efficacy and harms. Specifically, in the MERIT study, maraviroc failed to meet the criteria for non-inferiority compared with efavirenz for one of the co-primary outcomes in the preplanned analysis, and a higher proportion of maraviroc-treated patients, compared with efavirenz-treated patients, withdrew due to a lack of efficacy. In addition, the manufacturer assumed different NRTI background therapies for maraviroc and comparator antiretrovirals, which biases the results in favour of maraviroc. The daily cost of maraviroc plus tenofovir/emtricitabine is [confidential information removed at the request of the manufacturer] compared with $39.46 for efavirenz/tenofovir/emtricitabine (Atripla) and a range of $47.06 to $52.43 for other US Department of Health and Human Services preferred treatments.

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

Other Discussion Points:
- The Committee noted that for viral load, < 50 copies/mL is currently the clinically relevant threshold.
- The Committee considered that there are many efficacious agents indicated for use in patients with HIV-1 who are treatment naive.
- The standard test for determining HIV-1 tropism in Canada is now the V3 loop GTT. The sole clinical trial is limited by the use of a tropism assay different from that currently used. The post hoc subgroup patient populations identified with the ESTA and V3 loop GTT had been pre-screened with the original Trofile assay, which does not reflect current testing procedures.

CEDAC Members:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius

June 15, 2011 Meeting

Regrets:
One CEDAC member did not attend

Conflicts of Interest:
None

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. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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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