Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Celsentri, which is also called maraviroc, not be listed for patients with HIV type 1 (HIV-1) who are treatment naive (have not previously been treated for HIV-1).

Reason for the Recommendation:
The one study involving HIV-1 patients who were treatment naive did not achieve the expected results, based on the analysis that was planned before the start of the study. More specifically, the study failed to show that Celsentri was not worse than efavirenz (which is also called Sustiva) in terms of the percentage of patients achieving a viral load of less than 50 copies/mL at 48 weeks. In addition, a larger percentage of Celsentri-treated patients than those treated with efavirenz did not respond well to treatment, either because of virologic failure (failure to achieve the specified viral load) or viral rebound (increase in viral load after having previously achieved the specified level), at 96 weeks.

Background:
Celsentri is a type of HIV-1 treatment called a chemokine receptor 5 (CCR5) antagonist. It works by blocking a receptor called CCR5, which a certain type of HIV uses to enter cells in the blood. This virus type is called CCR5-tropic HIV-1. Health Canada has approved Celsentri for use with other anti-HIV medicines in adults with CCR5-tropic HIV-1 infection.

Celsentri is available as 150 mg and 300 mg tablets, which are taken by mouth. 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 other medications.

Submission History:
Celsentri was previously submitted to the Common Drug Review (CDR) in November 2007, but the submission was withdrawn before the CEDAC meeting took place. Following a resubmission, Celsentri was reviewed for the treatment of HIV-1 in adults who had already received treatment for HIV-1 and received a recommendation to list with criteria (see Notice of CEDAC Final Recommendation, November 12, 2008).

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Celsentri and a review of economic information prepared by the manufacturer of Celsentri. The manufacturer submitted a confidential price for Celsentri. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials
CEDAC reviewed one study of treatment-naive patients with CCR5-tropic HIV-1. The MERIT study was 96 weeks long and was designed to see if Celsentri was not worse than efavirenz. All patients in the study were also being treated with lamivudine plus zidovudine; lamivudine plus zidovudine is also called Combivir. The MERIT study was originally planned to include two Celsentri treatment groups (300 mg daily, and 300 mg twice daily) and an efavirenz 600 mg daily group. However, patients were no longer put on Celsentri 300 mg daily (after 177 patients were already put on this dose) because an interim analysis (analysis after only part of the study was complete) failed to show that Celsentri 300 mg daily was not worse than efavirenz. It was originally planned to have 1,071 patients in the study, but the decision to stop putting patients on Celsentri 300 mg daily left the total number of patients in the study at 740, and of this number, 721 were treated.

Patients included in the MERIT study had HIV-1, were treatment naive (defined as having no more than 14 days of HIV-1 treatment), and had a viral load of more than 2,000 copies/mL with only CCR5-tropic virus detected, using the original Trofile assay (a laboratory test to determine whether patients have CCR5-tropic virus). Later on, the manufacturer did additional analyses of the MERIT study using two different laboratory tests (enhanced sensitivity Trofile assay [ESTA] and the V3 loop genotype test [GTT]) to identify patients with CCR5-tropic virus. Use of these tests meant that 10% (ESTA) and 14% (V3 loop GTT) of the original group of patients included in the MERIT study would not be included. The V3 loop GTT is currently the standard test used in Canada for finding out whether a patient has CCR5-tropic virus.

A high percentage of patients stopped participating in the study (approximately 35%), which was similar for Celsentri and efavirenz. However, reasons for stopping participating were different depending on which treatment the patient received. Celsentri patients stopped participating mostly because the medication was not working, whereas the efavirenz patients stopped participating mostly because of side effects.

Outcomes
Outcomes of interest were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality (death), quality of life, viral load, CD4 counts, percentage of patients for whom the treatment did not work, stopping participating in the study, serious side effects, and side effects.

The two main purposes of the MERIT study were to measure the percentage of patients achieving a viral load of less than 400 copies/mL and less than 50 copies/mL at week 48. In either case, Celsentri would be considered not worse than efavirenz if it was unlikely that the estimated percentage of patients achieving the above viral loads was not more than 10% lower for Celsentri compared with efavirenz.

The Committee noted that there was a lack of quality of life data in the MERIT study.

Results

Efficacy or Effectiveness

- There were five deaths in MERIT, two in the Celsentri group, and three in the efavirenz group, none of which were due to HIV-1.
- When data from all patients who started the study were analyzed, the following results were noted: At week 48, fewer Celsentri-treated patients reached an undetectable viral load (defined as less than 50 copies/mL) than efavirenz, based on the original Trofile assay (65% versus 69%), and the results failed to show that Celsentri was not worse than efavirenz. Analyses based on the ESTA and V3 loop GTT showed that Celsentri was not worse than efavirenz. When data from only those patients who followed the study rules were analyzed, the results based on the original Trofile assay and ESTA were similar to the above; results based on the V3 loop GTT were not provided.
- When data from all patients who started the study were analyzed, Celsentri was not worse than efavirenz, in terms of the percentage of patients who were able to achieve a viral load of less than 400 copies/mL, based on any of the following: the original Trofile assay, ESTA, or V3 loop GTT. However, when only data from patients who followed the study rules were analyzed, the results failed to show that Celsentri was not worse than efavirenz, based on the original Trofile assay. Celsentri was shown to be not worse than efavirenz, based on the ESTA. Results based on the V3 loop GTT were not provided.
- At 96 weeks, more Celsentri patients than efavirenz patients did not respond well to treatment, due to virologic failure or viral rebound, based on both the original Trofile assay and the ESTA; results based on the V3 loop GTT were not provided.
- CD4 counts increased more in Celsentri-treated patients than efavirenz-treated patients, and this difference was found at both 48 weeks and 96 weeks, based on the original Trofile assay. Results were similar based on the ESTA.

Harms (Safety and Tolerability)

- The percentage of patients reporting a serious side effect, and reporting any side effect, was similar between Celsentri and efavirenz.
- The percentage of patients stopping participating due to a side effect was lower for Celsentri (6%) than efavirenz (16%). The most common side effect that caused the patient to stop taking part in the study was an increase in liver enzymes, for both Celsentri (seven patients) and efavirenz (11 patients).
- The overall occurrence of infections was similar for Celsentri- and efavirenz-treated patients in the MERIT study. There was no sign of an increase in cancer or increase in liver enzymes with Celsentri compared with efavirenz.

Cost and Cost-Effectiveness

The manufacturer submitted economic information comparing Celsentri with other HIV-1 treatments (efavirenz, atazanavir [also called Reyataz], darunavir [also called Prezista], lopinavir/ritonavir [also called Kaletra], and raltegravir [also called Isentress]) for treatment-naive patients with CCR5-tropic HIV-1 in Canada, to evaluate the health benefit.

The assumption that Celsentri had similar benefits and risks to other HIV-1 treatments was based on the results of some patients in the MERIT study (versus efavirenz), as well as analysis of results from a number of other studies (with other HIV-1 treatments). At the confidential submitted price for Celsentri, the manufacturer estimated that Celsentri costs more per month

than efavirenz and is cost saving compared with other HIV-1 treatments. [The manufacturer requested that details from its economic evaluation be removed from the previous sentence.]

A number of potential problems with the manufacturer's economic analysis were noted. The main problem is that there is a lack of data to support the assumption that Celsentri has similar benefits and risks to the other HIV-1 treatments. In particular, Celsentri was unable to show that it was not worse than efavirenz for one of the main results, and a higher percentage of Celsentri-treated patients than efavirenz-treated patients stopped taking part in the study because the treatment was not working. In addition, the manufacturer assumed different background treatments for Celsentri and the other HIV-1 drugs used as comparison treatments, which biases the results in favour of Celsentri. The daily cost of Celsentri plus tenofovir/emtricitabine is [confidential information removed at the request of the manufacturer], compared with $39.46 for efavirenz/tenofovir/emtricitabine (also called Atripla) and a range of $47.06 to $52.43 for other treatments preferred by the US Department of Health and Human Services.

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

Other Discussion Points:
- The Committee discussed that the goal for viral load is currently less than 50 copies/mL.
- The Committee considered that there are many drugs that work well and are 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. This is different from the original Trofile assay that was used to select patients to participate in the MERIT study. Using the ESTA and/or the V3 loop GTT after patients have been tested with the original Trofile assay is not generally done in medical practice.

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
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC

CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has requested the deletion of confidential information.