CEDAC FINAL RECOMMENDATION

DARUNAVIR
(Prezista™ – Janssen-Ortho Inc.)
New Indication: HIV-1 Treatment-Naive

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that darunavir be listed in treatment naive patients for whom protease inhibitor therapy is indicated.

Reasons for the Recommendation:
1. The Committee considered the results of a CDR systematic review that included a 96-week interim analysis of one open-label randomized controlled trial in treatment-naive patients with HIV-1 comparing darunavir boosted with ritonavir (800 mg/100 mg) to lopinavir boosted with ritonavir (800 mg/200 mg). There was a statistically significantly greater proportion of darunavir patients with HIV-1 RNA < 50 copies/mL compared with lopinavir patients at 96 weeks. Serious adverse events and withdrawals due to adverse events were significantly lower for darunavir compared with lopinavir.

2. Darunavir plus ritonavir (800 mg/100 mg) is similar in cost to lopinavir plus ritonavir (800 mg/200 mg). Whereas darunavir is similar in cost to other protease inhibitors, when considering patients who do not require protease inhibitor therapy, darunavir is more expensive than the non-nucleoside reverse transcriptase inhibitor, efavirenz (600 mg).

Background:
Darunavir is a protease inhibitor approved by Health Canada for the treatment of HIV-1 infection when co-administered with 100 mg ritonavir, together with other antiretroviral agents. The focus of this review is the use of darunavir in treatment-naive adults with HIV-1. Darunavir is available as a 300 mg, 400 mg and 600 mg tablet. The recommended dose in treatment-naive patients is 800 mg once daily.

Submission History:
Darunavir was previously reviewed by CEDAC for its use in treatment-experienced HIV-1 patients and received a recommendation to list (see Notice of CEDAC Final Recommendation, February 14, 2007). At that time, darunavir had a Notice of Compliance with Conditions from Health Canada.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of darunavir in treatment-naive patients with HIV-1 and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The CDR systematic review included one multicentre, open-label, randomized controlled trial (ARTEMIS) of 691 treatment-naive HIV-1 patients with plasma HIV-1 RNA > 5000 copies/mL. Darunavir 800 mg plus ritonavir 100 mg was compared with lopinavir 800 mg plus ritonavir 200 mg. All patients also received optimized background therapy consisting of tenofovir and emtricitabine. ARTEMIS is an ongoing 192 week study; reported results are from a 96-week pre-planned interim analysis.

ARTEMIS is limited by the open-label design and a high withdrawal rate (20%) that differed between darunavir and lopinavir groups (17% versus 23%). The lack of blinding is not likely to impact objective outcomes such as virologic response.

Outcomes
The primary outcome of ARTEMIS was the proportion of patients with plasma HIV-1 RNA <50 copies/mL. The non-inferiority of darunavir plus ritonavir compared with lopinavir plus ritonavir was evaluated. The non-inferiority margin was set at 12%. It was preplanned that if non-inferiority was established, superiority would also be evaluated.

In addition, the Committee discussed the following outcomes included in the CDR systematic review: virologic failure, change in CD4 cell count, treatment adherence and adverse events.

Results
Efficacy or Effectiveness
- In the intention-to-treat population, there was a statistically significantly greater proportion of darunavir patients with HIV-1 RNA < 50 copies/mL compared with lopinavir patients at 96 weeks [79% versus 71%, relative risk (RR) 1.12, 95% confidence interval (CI): 1.02 to 1.22, P = 0.01]. This was a preplanned interim analysis and whether superiority is maintained over the long-term is not yet known.
- There were statistically significantly fewer darunavir patients who experienced virologic failure compared with lopinavir patients. Virologic failure was defined as patients who did not achieve a viral load of < 50 copies/mL after 24 weeks of treatment or patients who achieved that level of response but subsequently rebounded to a measurable viral load.
- Changes in CD4 cell counts and treatment adherence (defined as taking >95% of study medication) were similar between the darunavir and lopinavir groups.

Harms (Safety and Tolerability)
- There were statistically significantly fewer darunavir patients compared with lopinavir patients who reported a serious adverse event (10% versus 16%, P = 0.02) or who withdrew due to an adverse event (4% versus 9%, P = 0.005).

- The proportion of patients reporting a lipid-related adverse event was statistically significantly lower in the darunavir group compared with the lopinavir group (8% versus 16%, P = 0.002). Interpretation of these results, however, is confounded by differences between treatment groups in ritonavir doses and the lack of standardization in the use of concomitant lipid-lowering therapies.
- The proportion of patients reporting gastrointestinal adverse events such as nausea, vomiting, or diarrhea was statistically significantly lower in the darunavir group compared with the lopinavir group. For part of the study, many patients were using an older formulation of lopinavir; it is not clear if this influenced these results.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the price of darunavir boosted with ritonavir to treatment regimens including protease inhibitors (lopinavir, atazanavir, fosamprenavir, and saquinavir) unboosted or boosted with ritonavir. A comparison of drug costs was justified by the manufacturer based on the finding from the ARTEMIS trial that darunavir is non-inferior to lopinavir based on the proportion of patients with HIV-1 RNA < 50 copies/mL.

Compared with other regimens including protease inhibitors, the daily cost of darunavir boosted with ritonavir (800 mg/100 mg, $21.61) is similar to lopinavir/ritonavir (800 mg/200 mg, $21.60), but more expensive than fosamprenavir/ritonavir (1400 mg/200 mg, $18.73) and less costly than atazanavir/ritonavir (300 mg/100 mg, $22.18). The daily cost of darunavir boosted with ritonavir is more expensive than regimens that include the non-nucleoside reverse transcriptase inhibitor, efavirenz (600 mg, $14.06).

Other Discussion Points:

- It was noted that because there is considerable experience with darunavir use for treatment-experienced patients infected with HIV-1, the harms profile is well-known.
- The Committee discussed the existence of several effective therapies for treatment-naive patients infected with HIV-1 and noted that viral resistance, drug interactions and harms limit some of these regimens so additional therapeutic options are desirable.
- The comparator that was evaluated in the ARTEMIS trial, lopinavir boosted with ritonavir, is currently considered one of the preferred first-line treatment options in international treatment guidelines, increasing the clinical relevance of the results of this trial.
- The Committee questioned whether the pre-specified non-inferiority margin of 12% for patients achieving HIV-1 RNA levels < 50 copies/mL was appropriate, but as superiority was demonstrated this was not a concern.

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. Michael Evans, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

None.

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

About this Document
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC Final Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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