



Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

DARUNAVIR

(Prezista – Janssen-Ortho Inc.)

New Indication: HIV-1, Treatment-Experienced (Pediatric)

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that darunavir be listed for use in treatment-experienced pediatric HIV-1 patients.

Reason for the Recommendation:

In one open-label uncontrolled trial conducted in treatment-experienced pediatric patients with HIV-1, darunavir improved virologic and immunologic outcomes compared with baseline and darunavir has been previously studied in large randomized controlled trials of treatment-experienced adults.

Background:

Darunavir, when co-administered with 100 mg ritonavir, and with other antiretroviral agents, has a Health Canada indication for the treatment of HIV infection. The focus of this CEDAC recommendation is the treatment of HIV-1 infection in treatment-experienced pediatric patients (six to 17 years of age and weighing at least 20 kg). Darunavir is a HIV protease inhibitor.

Darunavir is available in 75 mg, 300 mg, 400 mg, and 600 mg tablets. The recommended dose for pediatric patients is based on body weight and should not exceed the recommended adult dose of darunavir/ritonavir (600 mg/100 mg twice daily). For pediatric patients ≥ 20 kg to < 30 kg, the recommended darunavir/ritonavir dose is 375 mg/50 mg twice daily; for ≥ 30 kg to < 40 kg, it is 450 mg/60 mg twice daily; and for ≥ 40 kg, it is 600 mg/100 mg twice daily.

Submission History:

Darunavir was previously reviewed by CEDAC for use in treatment-experienced HIV-1 adult patients and treatment-naïve HIV-1 adult patients. It was recommended that darunavir be listed as an alternate protease inhibitor (PI) as part of a HIV treatment regimen for treatment-experienced adult patients who have demonstrated failure to multiple PIs and in whom less expensive PIs are not a treatment option (see Notice of CEDAC Final Recommendation, February 14, 2007). At that time, darunavir had a Notice of Compliance with Conditions from Health Canada. A Notice of Compliance was issued for darunavir in March 2009. Darunavir also

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received a recommendation to be listed in treatment-naïve patients for whom protease inhibitor therapy is indicated (see Notice of CEDAC Final Recommendation, October 14, 2009).

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of controlled and uncontrolled trials and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials

The CDR systematic review included one published, manufacturer-sponsored, uncontrolled, open-label study, DELPHI. The DELPHI study evaluated pharmacokinetic parameters in the initial two weeks of the study (part one) and the efficacy and harms of darunavir/ritonavir over 48 weeks (part two). In part two of the study, darunavir/ritonavir dosing followed the Health Canada recommended weight-based doses.

Patients included in part two of the DELPHI study were treatment-experienced children (six to < 12 years; n = 24) and adolescents (12 to < 18 years; n = 56) on a stable antiretroviral regimen, but with a viral load > 1,000 copies/mL. All patients had previously used at least three antiretroviral agents and most patients had baseline evidence of genotypic resistance. The median duration of time since diagnosis of HIV infection was 11 years and 50% of patients had Category C disease, as per the Centers for Disease Control and Prevention classification system. The majority of patients, 78%, had acquired HIV infection through perinatal transmission.

The overall withdrawal rate was 6.3%. The key limitation of the DELPHI study was the lack of a control group, although this design is often observed in pediatric studies of antiretroviral agents.

Outcomes

The primary outcome in part two of the DELPHI study was the proportion of patients with $\geq 1 \log_{10}$ reduction in viral load from baseline after 24 weeks. The Committee also discussed the proportion of patients with a viral load < 50 copies/mL, immunologic response, and adverse events.

Quality of life and HIV-related morbidity were not measured.

Results

Efficacy or Effectiveness

- The proportion of patients with a $\geq 1 \log_{10}$ reduction in HIV-1 viral load compared with baseline was 74% at 24 weeks and 65% at 48 weeks; 50% of patients at 24 weeks and 48% at 48 weeks had a viral load < 50 copies/mL.
- There were fewer severely immunosuppressed patients (CD4 count < 15%) at 48 weeks compared with baseline (17% versus 40% respectively) and fewer patients had a CD4 cell count below 200 cells/L (14.1% versus 31.3% respectively).

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- Resistance was evaluated in patients with viral rebound and who had baseline and end point genotyping (n = 16). Five of 16 (31%) patients had a darunavir resistance-associated mutation over the 48 weeks.
- Statistically significant increases in height were reported at 24 weeks and statistically significant increases in body mass index and weight were reported at 48 weeks.

Harms (Safety and Tolerability)

- The proportion of patients with more than one serious adverse event was 11% at 24 weeks and 14% at 48 weeks. There were no deaths.
- There was one report of hepatitis A, two reports of elevations of low-density lipoprotein, two reports of cardiovascular adverse events (both considered unrelated to study drug), and two pancreas-related adverse events during the study.
- One (1.3%) patient withdrew because of an adverse event.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of darunavir/ritonavir and the antiretroviral comparators: atazanavir, fosamprenavir, or lopinavir, each boosted with ritonavir; nelfinavir without ritonavir; and enfuvirtide. The manufacturer concluded that the cost per day of darunavir/ritonavir is higher than other protease inhibitors, but lower than enfuvirtide.

The daily cost of darunavir/ritonavir ranges from \$19.27 to \$31.57, depending on patient weight, for HIV-1 infected treatment-experienced pediatric patients, which is less than the daily cost of enfuvirtide (\$40.39 to \$80.78). Enfuvirtide is the only other antiretroviral agent with a Health Canada indication for use in this patient population.

Other Discussion Points:

- It was noted that the DELPHI study was an uncontrolled open-label study with limited statistical analyses performed, but this design is in keeping with regulatory requirements for pediatric patients when a drug is to be used for the same indication as has been studied and approved in adults. Similar study designs have been used to support pediatric indications for other antiretroviral therapies.
- The Committee considered that there are few antiretroviral agents that have been studied in treatment-experienced pediatric patients with HIV and that there is an unmet need with respect to antiretroviral treatment options for these patients.
- The Committee noted that additional factors considered in the treatment of children with HIV include the ability to swallow pills, the need for formulations that are both age and palate-appropriate, the complexity of regimen, and the toxicity. A darunavir oral suspension is currently in development.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Michael Allan, 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. Kelly Zarnke.

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Regrets:

Dr. Anne Holbrook (Vice-Chair) and Dr. Ken Bassett.

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. 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The 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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