

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

DEFERASIROX (Exjade™ – Novartis Pharmaceuticals Canada Inc.)

Description:

Deferasirox is an oral iron chelator that has received a Notice of Compliance with Conditions (NOC/c) from Health Canada. Deferasirox is approved for use in the management of chronic iron overload in:

- patients with transfusion-dependent anemias aged six years or older;
- patients with transfusion dependent anemias aged two to five who cannot be adequately treated with deferoxamine.

Dosage Forms:

125, 250 and 500 mg tablets. The recommended initial daily dose of deferasirox is 10, 20 or 30 mg/kg/day, depending on the patient's transfusion rate and the goal of treatment.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that deferasirox be listed for patients who require iron chelation but in whom deferoxamine is contraindicated.

Reasons for the Recommendation:

1. While deferasirox has been shown to be effective in reducing iron stores in patients with chronic iron overload, it is uncertain if it is as effective and it may be associated with more adverse events as compared with deferoxamine. However, the Committee recognized the need for a treatment alternative in patients for whom deferoxamine is not a therapeutic option due to contraindications.
2. The daily cost of deferasirox ranges from \$40 to \$158 and this is significantly greater than the cost of deferoxamine (\$20 to \$84 per day). An economic evaluation submitted by the manufacturer, reported an incremental cost-effectiveness of deferasirox of \$67,595 per quality adjusted life year (QALY). However the evaluation assumed an improved quality of life and higher rate of treatment compliance with deferasirox versus deferoxamine, and this has not been demonstrated in clinical trials.

Summary of Committee Considerations:

The Committee considered a systematic review of three RCTs comparing deferasirox with deferoxamine in patients with chronic iron overload. Two of these RCTs, a 48 week study in 71 patients with β -thalassemia and a 48 week study of 195 patients with sickle cell disease, were designed with a primary endpoint of safety and tolerability.

Common Drug Review

The third RCT considered by the Committee was a 12 month non-inferiority trial in 591 patients with β -thalassemia in which the primary outcome was the successful reduction in liver iron content (LIC) as assessed by either liver biopsy or a Superconducting Quantum Interference Device (SQUID). The overall success rate in achieving target LIC levels was reached in 53% of patients treated with deferasirox versus 66% of patients treated with deferoxamine and this difference did not meet the predefined non-inferiority threshold. A subgroup analysis reported no difference in the success rate in achieving target LIC levels in patients with a baseline LIC \geq 7mg Fe/g dry weight who received deferasirox in doses of 20 mg/kg or 30 mg/kg daily (n=185) compared to those who received deferoxamine treatment (n=186) (success rates of 59% in each group).

At the end of the pivotal study, there were statistically significant differences in favour of deferasirox in the proportion of patients who were satisfied or very satisfied with treatment (85% vs. 39%, respectively), found the treatment to be more convenient (93% vs. 11%, respectively) and were willing to continue with their treatment (86% vs. 14%, respectively).

The most frequently observed adverse effects of deferasirox include gastrointestinal upset, skin rash and elevation of serum creatinine. Deferasirox patients experienced numerically higher rates of abdominal pain, diarrhea, nausea and vomiting than patients treated with deferoxamine. Additionally, increases in serum creatinine of $>33\%$ at two or more consecutive post baseline visits occurred at a greater frequency in deferasirox treated patients compared to deferoxamine treated patients (38% vs 14%, respectively) in the largest RCT. A March 9, 2007 letter from the manufacturer to health professionals suggests a contributory role of deferasirox in the development of acute renal failure, including some cases with a fatal outcome. It is recommended that serum creatinine be measured twice before initiating therapy, weekly for the first month of therapy or after dosing changes, and monthly thereafter. Monthly testing for proteinuria is also recommended.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.