

## Recommendations and Reasons

Committee to Evaluate Drugs (CED)

# Deferasirox

### Product:

Deferasirox (Exjade®)  
125mg, 250mg and 500mg tablets

### Class of drugs:

Iron chelating agent

### Indication:

Treatment of chronic iron overload

### Manufacturer:

Novartis Pharmaceutical Canada Inc.

## CED Recommendation-

The CED recommended that deferasirox (Exjade) be funded through the Exceptional Access Program on the basis that deferasirox (Exjade) provides a treatment alternative in patients for whom deferoxamine is not a therapeutic option.

## Executive Officer Decision

Following the CED's recommendation and based on a subsequent agreement with the manufacturer that addresses price, the Executive Officer decided to fund deferasirox (Exjade) through the EAP according to specific criteria.

## Status

Funding available through the Ontario Public Drug Programs via the EAP.

### Highlights of Recommendation:

- ◆ Deferasirox (Exjade) is a drug used to reduce excess iron levels in patients with on-going iron overload, usually resulting from frequent blood transfusions required to treat thalassemia, sickle cell disease or myelodysplastic syndrome (MDS).
- ◆ The Committee reviewed three clinical studies that compared deferasirox (Exjade) with deferoxamine, an alternative treatment for iron overload. The studies were conducted in patients with thalassemia or sickle cell disease.
- ◆ Study results indicated that deferasirox (Exjade) is effective in reducing iron stores. However, the study findings were unclear as to whether deferasirox (Exjade) is as effective as deferoxamine. Deferasirox (Exjade) may be associated with more adverse effects compared with deferoxamine.
- ◆ The Committee also examined the use of deferasirox (Exjade) in patients with MDS and noted that certain MDS patients may benefit from therapy.
- ◆ Deferasirox (Exjade) is considerably more expensive than deferoxamine (\$60 - \$158 per day versus \$26 - \$112 per day).
- ◆ **Overall, the Committee recognized that deferasirox (Exjade) provides a treatment alternative in patients for whom deferoxamine is not a therapeutic option. Therefore, the CED recommended that this product be considered through the Exceptional Access Program according to specific criteria.**

### Background:

Deferasirox (Exjade) is an oral drug used to treat patients who have excess iron levels in their bodies, usually due to blood transfusions or genetic disorders. Extra iron can build up in the organs and cause heart failure, liver disease and diabetes.

Deferasirox (Exjade) is indicated in the management of chronic iron overload in patients with transfusion-dependent anemias. Prior to Deferasirox (Exjade), deferoxamine has been the only drug available in Canada used for this indication. Deferoxamine is administered via injection and is usually given subcutaneously through a pump for 10 to 12 hours at night.

### Detailed Discussion:

- ◆ The Committee evaluated deferasirox (Exjade) for the management of chronic iron overload in patients with thalassemia, sickle cell disease, myelodysplastic syndrome (MDS) and other rare anemias.
- ◆ Published trials for deferasirox (Exjade) were limited to patients with thalassemia or sick cell disease. Clinical studies in patients with MDS or other rare anemias are not available.
- ◆ Three trials were reviewed:
  - ◇ Trial 0105 (Piga et al. Haematologica 2006;91(7):873-80) was a safety and tolerability study in thalassemia patients;
  - ◇ Trial 0107 (Cappellini et al. Blood 2006;107(9):3455-62) was a non-inferiority study in thalassemia patients;
  - ◇ Trial 0109 (Vichinisky et al. BJH 2006;136:501-508) was a safety and tolerability study in patients with sickle cell disease.
- ◆ Data from the three trials showed no improvements in mortality or serious adverse events for deferasirox (Exjade) compared to deferoxamine in transfusion dependent thalassemia patients or patients with sickle cell disease.

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- ◆ In Trial 0107, the overall success rate in achieving target liver iron content (LIC) levels was 53% in patients treated with deferasirox (Exjade) versus 66% in patients treated with deferoxamine. This difference did not meet the pre-defined **non-inferiority** threshold, that is comparable efficacy was not demonstrated.
- ◆ In Trial 0109, deferasirox (Exjade) and deferoxamine had a similar effect on LIC in the overall study population. Deferasirox (Exjade) and deferoxamine had a similar effect on LIC in patients with baseline LIC above 7mg Fe/g dw; however, the relative effects of deferasirox (Exjade) in patients with baseline LIC below 7mg Fe/g dw were less marked.
- ◆ There were no reliable quality of life data for any of the trials. Patient-reported satisfaction was higher for deferasirox (Exjade) in patients in Trial 0107 and 0109, but the validity of the patient satisfaction measures were not reported. The number of patients who withdrew due to an adverse event was numerically higher in the deferasirox (Exjade) arm (not statistically significant), compared to the deferoxamine arm, in all three trials.
- ◆ The most frequently observed adverse effects of deferasirox (Exjade) included gastrointestinal upset, skin rash, and elevation of serum creatinine. Deferasirox (Exjade) patients experienced numerically higher rates of abdominal pain, diarrhea, nausea, and vomiting than patients treated with deferoxamine.
- ◆ Health Canada has released a warning regarding the risk of acute renal failure associated with deferasirox (Exjade). ([http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2008/exjade\\_2\\_pc-cp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2008/exjade_2_pc-cp-eng.php))
- ◆ With respect to the potential place in therapy of deferasirox (Exjade) in the setting of MDS, the Committee noted that generally, survival and quality of life of MDS patients are primarily affected by leukemic transformation and infection (Tefferi, A., *Iron Chelation Therapy for MDS: If and When*. *Mayo Clin Proc*. Feb 2006).
- ◆ Patients suffering from MDS tend to be older and have more co-morbid conditions in comparison to patients suffering from thalassemia or sickle cell disease. The median age of diagnosis of MDS is 65 years old, and overall survival is less than 5 years. No high quality evidence is available to implicate transfusional hemosiderosis (iron accumulation due to transfusion) as a

major determinant of survival, and no controlled studies indicate that this particular complication can be avoided with iron chelation therapy (Tefferi, A. *Mayo Clin Proc*. Feb 2006). It is unlikely that iron chelation therapy would benefit patients with MDS whose median survival is estimated at less than 5 years. Nevertheless, the Committee acknowledged the adverse impact associated with chronic iron overload and considered whether there are subsets of the MDS population that would benefit from an oral iron chelation therapy. It was noted that patients with low risk MDS may benefit from the use of deferasirox (Exjade) (Greenberg, P. *MDS: Iron Overload Consequences and Current Chelating Therapies*. *J of National Comprehensive Cancer Network*. Jan 2006). Iron chelation is less likely to be useful for individuals with high risk disease because clinical issues other than tissue siderosis are generally more prominent (e.g. hematopoietic failure, potential progression to acute myeloid leukemia).

- ◆ The daily cost of deferasirox (Exjade) ranges from \$60 - \$158 (based on a 70 kg patient). This is significantly more expensive than deferoxamine, at \$26 - \$112/day.
- ◆ The manufacturer's pharmacoeconomic evaluation assumed an improved quality of life and higher rate of compliance with deferasirox (Exjade) versus deferoxamine; these assumptions are speculative.
- ◆ **Overall, the Committee noted that deferasirox (Exjade) has been shown to be effective in reducing iron stores in patients with chronic iron overload; however, it is uncertain whether it is as effective as deferoxamine and it may be associated with more adverse events. The Committee recognized the need for a treatment alternative in patients for whom deferoxamine is not a therapeutic option.**

#### EAP Criteria:

Deferasirox (Exjade) is funded through the Exceptional Access Program (EAP) according to the following criteria:

*For the management of chronic iron overload in transfusion related anemia due to B-thalassemia or sickle cell disease in patients who are 6 years of age or older;*  
OR

*For the management of chronic iron overload in transfusion related anemia due to B-thalassemia or sickle cell disease, in patients who are 2 to 5 years of age, who cannot be adequately treated with deferoxamine.*

#### NOTE:

1. *Combination therapy (deferasirox in addition to another iron chelating agent) will not be approved.*
2. *Therapy should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.*

#### Renewal criteria:

*The patient continues to require iron chelation therapy and has had a consistent response to therapy (demonstrated by a reduction in baseline LIC levels).*

*The following documentation is required:*

1. *A transfusion record from the past year AND*
2. *LIC levels – baseline (pre-treatment) and since initiation of treatment. The most recent LIC levels should be from within the previous year.*

#### CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

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



Ministry of  
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