Health Canada Endorsed Important Safety Information on
[Pr]EXJADE* (deferasirox)

NOVARTIS

November 30, 2009

Dear Health Care Professional:

Subject: Use of EXJADE* (deferasirox) in Patients Diagnosed with Myelodysplastic Syndrome (MDS) and in Elderly Patients regarding Renal Events and Gastrointestinal Hemorrhage (Fatal in Rare Cases)

EXJADE* (deferasirox) is indicated in the management of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older. EXJADE* is also indicated in the management of chronic iron overload in patients with transfusion-dependent anemias aged two to five who cannot be adequately treated with deferoxamine.

Therapy with EXJADE* should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

- Review of adverse events for patients treated with EXJADE* suggests a greater risk of kidney failure, gastrointestinal hemorrhage (potentially fatal) and deaths in patients with myelodysplastic syndrome (MDS) and in elderly patients compared to younger patients with other chronic anemias such as β-thalassemia and sickle cell disease. Many of the adverse events reported are common to elderly patients and patients with MDS, making it difficult to draw any conclusions.

- Novartis has proposed changes to the Canadian Product Monograph, including a contraindication in high risk myelodysplastic syndrome (MDS) patients and those with advanced malignancies because these patients are not likely to benefit from iron chelation therapy due to the expected rapid progression of their disease.

- Risk factors for kidney failure include pre-existing compromised renal function, and it is therefore recommended that creatinine clearance (and/or serum creatinine) be assessed twice before initiating therapy. Weekly monitoring of creatinine clearance (and/or serum creatinine) is recommended in the first month after initiation or modification of therapy, and monthly thereafter. In addition to the existing creatinine clearance contraindication of <60 mL/min, Novartis has proposed to include a contraindication of serum creatinine >2 times the age-appropriate upper limit of normal.

- Gastrointestinal hemorrhage is a known adverse reaction of EXJADE*. There have been rare reports of fatal gastrointestinal hemorrhage, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts.

In the review of death cases in the MDS patient population, it was apparent that approximately two-thirds of the deaths were in patients who had received less than six months of therapy, indicating that patients with advanced disease and a corresponding poor prognosis have been treated with EXJADE*. These patients are unlikely to derive benefit from treatment with EXJADE*.

In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients, and therefore should be monitored closely for adverse reactions that may require a dose adjustment.

Novartis has proposed changes to the Canadian Product Monograph that are currently under review by Health Canada. The proposed changes include (but are not limited to) the following:

- EXJADE* is contraindicated in high risk myelodysplastic syndrome (MDS) patients, any other MDS patient with a life expectancy < 1 year, and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

- In addition to monitoring serum creatinine, it is now also recommended that creatinine clearance be assessed twice before initiating therapy. Weekly monitoring of creatinine clearance (and/or serum creatinine) is recommended in the first month after initiation or modification of therapy, and monthly thereafter. EXJADE* is contraindicated in patients with serum creatinine >2 times the age-appropriate upper limit of normal.

Managing marketed health product related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or unexpected adverse reactions in patients receiving EXJADE* should be reported to Novartis or Health Canada at the following addresses:

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, (QC) H9S 1A9
Phone: 1-877-631-6775 x 3425 (Drug Safety & Epidemiology)

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Metabolism, Oncology and Reproductive Sciences
Therapeutic Products Directorate
BMORS_Enquiries@hc-sc.gc.ca
Tel: (613) 941-3171 Fax: (613) 941-1365

Your professional commitment in this regard has an important role in protecting the well being of your patients by contributing to early signal detection and informed drug use.

Should you have medical enquiries regarding EXJADE*, please contact our Medical Information Department at 1-800-363-8883.

For more information please consult the EXJADE* Prescribing Information and Consumer Information on our Website (www.novartis.ca).

Sincerely,

Original signed by

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Jean-Marie Leclerc, M.D. FRCP(C)
Chief Scientific Officer and Senior Vice-President Clinical and Regulatory Affairs

*EXJADE is a registered trademark.