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

NOVARTIS

March 4, 2008

Dear Health Care Professional:

Subject: Reports of Hepatic Failure with EXJADE* (deferasirox)

Following discussions with Health Canada, Novartis wishes to provide you with updated safety information regarding reports of hepatic failure with EXJADE* (deferasirox).

EXJADE* 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.

- Cases of hepatic failure (some with a fatal outcome) have been reported internationally following post-marketing use of EXJADE*. Most of these cases involved patients with significant comorbidities including liver cirrhosis and multi-organ failure.
- As indicated in the currently approved EXJADE* Product Monograph, it is recommended that liver function tests be monitored monthly. If there is an unexplained, persistent and progressive increase in serum transaminase levels, EXJADE* treatment should be interrupted.

Recently, a post-marketing report of hepatic failure with encephalopathy was communicated to the FDA by a patient in the U.S. who had received EXJADE* for five days. The patient's hospital records indicate that the patient had a history of alcohol use and had slightly abnormal liver function tests prior to starting EXJADE* therapy. In addition, the patient was treated for a non-approved indication with a serum ferritin level that was > 10-fold lower than is recommended in the approved EXJADE* label to initiate therapy. EXJADE* therapy was stopped and the patient recovered. Based on the information available, the potential role of EXJADE* cannot be excluded, however, after review of this case, Novartis and external medical experts agree that there are extenuating circumstances around this case.

As of October 31, 2007, the total cumulative exposure to EXJADE* was estimated to be 36,797 patients: 31,444 exposed to marketed EXJADE* and 5,353 patients in clinical trials. There are a total of 24 international reports of hepatic failure - 21 post-marketing reports and 3 reports from clinical studies. Two of the 24 cases were reported in Canada. Most reports of hepatic failure involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure. No patient with normal baseline liver function or without additional life-threatening complications of their underlying disease has developed hepatic failure.

EXJADE* has not been studied in patients with hepatic impairment and must be used with caution in hepatic impaired patients.

Although a causal relationship between EXJADE* and hepatic failure has not been established, the Product Monograph for EXJADE*, under **WARNINGS AND PRECAUTIONS**: **Hepatic/Biliary/Pancreatic** section has been updated to include this important safety information as follows:

> There have been postmarketing reports of hepatic failure in patients treated with EXJADE*. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

In addition, the **ADVERSE REACTIONS: Post-Market Adverse Drug Reactions** section has been updated to include "hepatic failure."

The Product Monograph has also been updated to include the following information to the **DOSAGE AND ADMINISTRATION** section.

> The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

Managing marketed health product related adverse reactions depends on health care professionals and consumers reporting them, in addition to reports collected from clinical trials. 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 serious or unexpected adverse events 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: 1-800-363-8883 (Medical Information)

Any suspected adverse reaction can also be reported to:
Canada Vigilance Program
Marketed Health Products Directorate, HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866-234-2345 Fax: 866-678-6789
CanadaVigilance@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

For other inquiries, please refer to contact information:
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

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

Pr EXJADE* is a registered trademark.