NOVARTIS

Important Information about Exjade® (deferasirox)
Tablets for Oral Suspension

IMPORTANT DRUG WARNING

DATE: May 14, 2007

Dear Healthcare Provider (or Doctor):

Novartis is writing to summarize the December 2006 changes made to the **WARNINGS** and **ADVERSE REACTIONS** sections of the Exjade® (deferasirox) Tablets for Oral Suspension prescribing information.

Exjade (deferasirox) is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

Further studies are being performed to determine the long-term benefits and risks of Exjade.

As Novartis is committed to providing you with up-to-date information regarding Exjade, this letter provides additional context to information that you may have previously received via the mailed prescribing information update card, at meetings or in discussions with your Exjade sales specialist and reiterates the important changes made to the prescribing information.

In the U.S. Package Insert for Exjade, the following information has been added to the **WARNINGS** section.

Renal
Cases of acute renal failure, some with a fatal outcome, have been reported following the postmarketing use of Exjade® (deferasirox). Most of the fatalities occurred in patients with multiple co-morbidities and who were in advanced stages of their hematological disorders. Particular attention should be given to monitoring serum creatinine in patients who: are at increased risk of complications, have preexisting renal conditions, are elderly, have co-morbid conditions, or are receiving medicinal products that depress renal function.

Serum creatinine should be assessed in duplicate before initiating therapy to establish a reliable pre-treatment baseline, due to variations in measurements. Serum creatinine should be monitored monthly thereafter. Patients with additional renal risk factors (see above) should be monitored weekly during the first month after initiation or modification of therapy, and monitored monthly thereafter.

Cytopenias (formerly Pancytopenia)
There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia, in patients treated with Exjade. Some of these patients died. The relationship of these episodes to treatment with Exjade is uncertain. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure. (See ADVERSE REACTIONS.) In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Interruption of treatment with Exjade should be considered in patients who develop unexplained cytopenia.

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Reintroduction of therapy with Exjade may be considered, once the cause of the cytopenia has been elucidated.

In the U.S. Package Insert for Exjade, the following information has been added to the **ADVERSE REACTIONS** section.

Postmarketing Experience.

The following adverse reactions have been spontaneously reported during post-approval use of Exjade. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

There have been reports of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia, in patients treated with Exjade. Although most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure, a contributory role for Exjade cannot be excluded. Cases of acute renal failure have been reported in the context of severe complications relating to the underlying disease. (See WARNINGS.)

Skin and subcutaneous tissue disorders: leukocytoclastic vasculitis, urticaria.
Immune system disorders: hypersensitivity reactions (including anaphylaxis and angioedema).

Important safety information
Exjade is contraindicated in patients with hypersensitivity to deferasirox or to any other component of Exjade.

Serum creatinine should be assessed in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Serum creatinine should be monitored monthly thereafter. Patients with preexisting renal conditions or patients who are receiving medicinal products that depress renal function should be monitored weekly during the first month after initiation or modification of therapy, and monthly thereafter. Nonprogressive increases in serum creatinine have been noted in 38% of Exjade-treated patients, compared to 14% of deferoxamine-treated patients, and appear to be dose related. These increases were within the normal range in 94% of patients. Exjade dosages had been adjusted once serum creatinine elevations were detected during the study.

Dose reduction, interruption, or discontinuation should be considered for elevations in serum creatinine. If there is a progressive increase in serum creatinine beyond the age-appropriate upper limit of normal, Exjade should be interrupted. Once the creatinine has returned to within the normal range, therapy with Exjade may be reinitiated at a lower dose followed by gradual dose escalation, if the clinical benefit is expected to outweigh potential risks.

Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of Exjade-treated patients, compared to 7.2% of deferoxamine-treated patients in Study 1, and monthly monitoring is recommended.

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Liver function should be monitored monthly, and if there is an unexplained, persistent, or progressive increase in serum transaminase levels, treatment with Exjade should be interrupted or discontinued. In Study 1, seventeen (5.7%) patients treated with Exjade developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits vs five (1.7%) patients treated with deferoxamine. Hepatic dysfunction associated with Exjade administration has been described in postmarketing reports.

Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Exjade, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, Exjade should be discontinued and appropriate medical intervention instituted.

Auditory (high-frequency hearing loss, decreased hearing) and ocular (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) disturbances have been reported with Exjade therapy in less than 1% of patients in clinical trials. Auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) are recommended before the start of Exjade treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, dose reduction or interruption should be considered.

Skin rashes may occur during treatment with Exjade. For rashes of mild to moderate severity, Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rashes where interruption of treatment may be necessary, Exjade may be reintroduced at a lower dose and gradually escalated after resolution of the rash. Reintroduction of Exjade at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.

The most frequently occurring adverse events with Exjade included diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, cough, and increases in serum creatinine. Maintenance of adequate hydration for patients experiencing diarrhea or vomiting is recommended. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related. These commonly reported adverse events were predominantly mild to moderate in severity with serious adverse events reported in 9.1% of patients in the EXJADE arm and 8.6% of patients in the deferoxamine arm.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of Exjade® to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover NJ 07936 or by phone (888-NOW NOVARTIS or 888 669 6682) or the internet at http://www.novartis.com

The Medical Community can further our understanding of adverse events by reporting all cases to the Agency via the MedWatch program by phone at 1-800- FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch or by mail:

MEDWATCH
Food and Drug Administration
5600 Fishers Lane
Rockville
MD 20852-9787

Please see enclosed revised Package Insert for complete prescribing information for Exjade® (deferasirox) Tablets for Oral Suspension.

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Please contact Novartis Oncology Medical Information, Communication and Education at 1-888-669-6682 if you have further questions.

Sincerely,

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