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

IMPORTANT DRUG WARNING

DATE: February 17, 2010

Dear Healthcare Provider (or Doctor):

Novartis Oncology is committed to providing you with up-to-date information regarding Exjade® (deferasirox) Tablets for Oral Suspension. This letter is to inform you about important updates to the Exjade prescribing information which are intended to provide additional guidance on patient monitoring and to ensure appropriate use of Exjade.

As a reminder, 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.

Changes to the Exjade Prescribing Information

The following new language (indicated in **bold**) has been added to the Contraindications, Warnings and Precautions, and Drug Interactions sections of the U.S. Exjade prescribing information along with a boxed warning. The updated full prescribing information, which incorporates these changes as well as additional changes, is enclosed for your reference.

BOXED WARNING:

WARNING: RENAL, HEPATIC FAILURE AND/OR GASTROINTESTINAL HEMORRHAGE

Exjade may cause:

- **renal impairment, including failure**
- **hepatic impairment, including failure**
- **gastrointestinal hemorrhage**

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes (MDS), underlying renal or hepatic impairment or low platelet counts (<50 x 10^9/L) [*see Contraindications (4), Warnings and Precautions (5.1- 5.7)*].
Exjade therapy requires close patient monitoring, including measurement of:

- **serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter;**
- **serum transaminases and bilirubin prior to initiation of therapy, every two weeks during the first month and monthly thereafter.**

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4 CONTRAINDICATIONS

Exjade is contraindicated in patients with:

- **creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal;**
- **poor performance status and high-risk myelodysplastic syndromes or advanced malignancies [*see Warnings and Precautions (5.7)*];**
- **platelet counts <50 x 10^9/L;**
- known hypersensitivity to deferasirox or any component of Exjade.

5 WARNINGS AND PRECAUTIONS

5.1 Renal

Acute renal failure, fatal in some patients **and requiring dialysis in** others, has been reported following the postmarketing use of Exjade (deferasirox). Most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. Monitor serum creatinine **and/or creatinine clearance** in patients who: are at increased risk of complications, have preexisting renal conditions, are elderly, have comorbid conditions, or are receiving medicinal products that depress renal function. **Closely monitor the renal function of patients with creatinine clearances between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.**

Assess serum creatinine **and/or creatinine clearance** in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Monitor serum creatinine **and/or creatinine clearance** monthly thereafter. In patients with additional renal risk factors (see above), monitor serum creatinine **and/or creatinine clearance** weekly during the first month after initiation or modification of therapy and monthly thereafter.

…There have also been reports of renal tubulopathy in patients treated with Exjade. **The majority of these patients were children and adolescents with ß-thalassemia and serum ferritin levels <1500 mcg/L.**

5.3 Gastrointestinal

Fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts, have been reported. Non-fatal upper GI irritation**,** ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Exjade…

5.6 Rash

…Erythema multiforme has been reported during Exjade treatment.

5.7 Co-morbidities

Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed. Exjade has been shown to decrease serum ferritin and liver iron concentration in clinical trials. Consider the importance of these factors as well as individual patient factors and the prognosis associated with any underlying conditions before initiation of Exjade therapy [*see Contraindications (4)*].

In postmarketing experience, there have been reports of serious adverse reactions, some with a fatal outcome, in patients taking Exjade therapy, predominantly when the drug was administered to patients with advanced age, complications from underlying conditions or very advanced disease. Most of these deaths occurred within six months of Exjade initiation and generally involved worsening of the underlying condition. The reports do not rule out the possibility that Exjade may have contributed to the deaths.

7.5 Interaction with Cholestyramine

The concomitant use of Exjade with cholestyramine may result in a decrease in Exjade efficacy. In healthy volunteers, the administration of cholesytramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC). Avoid the concomitant use of cholestyramine with Exjade. If you must co-administer these agents together, consider increasing the initial dose of Exjade to 30 mg/kg and monitor serum ferritin levels and clinical responses for further dose modification [*see Dosage and Administration (2.2)*].

Updated Important Safety Information

Based on the revisions to the Exjade prescribing information, Novartis has updated the important safety information as follows:

Important safety information about Exjade

EXJADE is contraindicated in patients with:

- Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal;
- Poor performance status and high-risk myelodysplastic syndromes or advanced malignancies
- Platelet counts <50 x 10^9/L;
- Known hypersensitivity to deferasirox or to any other component of EXJADE.

Renal

Acute renal failure, fatal in some patients and requiring dialysis in others, has been reported following the postmarketing use of EXJADE. Most of the fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematologic disorders. Monitor serum creatinine and/or creatinine clearance in patients who: are at increased risk of complications, have pre-existing renal conditions, are elderly, have comorbid conditions, or are

receiving medicinal products that depress renal function. Closely monitor the renal function of patients with creatinine clearances between 40 and less than 60 mL/min, particularly in situations where patients have additional risk factors that may further impair renal function such as concomitant medications, dehydration, or severe infections.

Assess serum creatinine and/or creatinine clearance in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Monitor serum creatinine and/or creatinine clearance monthly thereafter. In patients with additional renal risk factors (see above), monitor serum creatinine and/or creatinine clearance weekly during the first month after initiation or modification of therapy and monthly thereafter.

Consider dose reduction, interruption, or discontinuation for increases in serum creatinine. For adult patients, reduce the daily dose of EXJADE by 10 mg/kg if a rise in serum creatinine to >33% above the average of the pretreatment measurements is seen at 2 consecutive visits, and cannot be attributed to other causes. For pediatric patients, reduce the dose by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at 2 consecutive visits. If there is a progressive increase in serum creatinine beyond the age-appropriate upper limit of normal, interrupt EXJADE use. 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.

Hepatic
There have been postmarketing reports of hepatic failure, some with a fatal outcome, in patients treated with EXJADE. Most of these events occurred in patients greater than 55 years of age. Most reports of hepatic failure involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure. Serum transaminases and bilirubin should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.

Gastrointestinal
Fatal gastrointestinal (GI) hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts, have been reported. Non-fatal upper GI irritation, ulceration, and hemorrhage have been reported in patients, including children and adolescents, receiving EXJADE. Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. Use caution when administering EXJADE in combination with drugs that have ulcerogenic or hemorrhagic potential, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants.

Cytopenias
There have been postmarketing reports 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 pre-existing hematologic disorders that are frequently associated with bone marrow failure. Monitor blood counts regularly. Consider interrupting treatment with EXJADE in patients who develop unexplained cytopenia. Reintroduction of therapy with EXJADE may be considered once the cause of the cytopenia has been elucidated.

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Hypersensitivity
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, discontinue EXJADE and institute appropriate medical intervention.

Rash
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. In severe cases, EXJADE may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration. Erythema multiforme has been reported during EXJADE treatment.

Co-morbidities

Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed. Exjade has been shown to decrease serum ferritin and liver iron concentration in clinical trials. Consider the importance of these factors as well as individual patient factors and the prognosis associated with any underlying conditions before initiation of Exjade therapy [see Contraindications (4)].

In postmarketing experience, there have been reports of serious adverse reactions, some with a fatal outcome, in patients taking Exjade therapy, predominantly when the drug was administered to patients with advanced age, complications from underlying conditions or very advanced disease. Most of these deaths occurred within six months of Exjade initiation and generally involved worsening of the underlying condition. The reports do not rule out the possibility that Exjade may have contributed to the deaths.

Special Senses
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, consider dose reduction or interruption.

Adverse Reactions
The most frequently occurring adverse reactions with a suspected relationship to EXJADE were diarrhea, vomiting, nausea, abdominal pain, skin rash, 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.

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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 (1-888-NOW-NOVA) 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

Enclosed please find the revised Package Insert for complete prescribing information for Exjade® (deferasirox) Tablets for Oral Suspension.

Please feel free to contact Novartis Oncology Medical Information at 1-888-NOW-NOVA if you have further questions.

Sincerely,
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