HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXJADE safely and effectively. See full prescribing information for EXJADE.

EXJADE® (deferasirox) tablets, for oral suspension
Initial U.S. Approval: 2005

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

See full prescribing information for complete boxed warning

Exjade may cause:
- **renal toxicity, including failure (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

Exjade therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.3, 5.7, 5.8) 07/2015

----------INDICATIONS AND USAGE----------

Exjade is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). An improvement in survival or disease-related symptoms has not been established. (1.1)

Exjade is indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established. (1.2)

Limitation of Use
Controlled clinical trials of Exjade in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed. (1.3)

The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- In patients with transfusional iron overload, the recommended initial daily dose is 20 mg per kg body weight once daily, as oral suspension. Calculate dose to the nearest whole tablet. (2.1)
- In patients with NTDT syndromes, the recommended initial daily dose is 10 mg per kg body weight once daily, as oral suspension. Calculate dose to the nearest whole tablet. (2.2)
- Monitor serum ferritin monthly and adjust dose accordingly. (2.1, 2.2)
- Monitor LIC every 6 months and adjust dose accordingly. (2.2)
- Do not chew or swallow tablets whole. (2.3)
- Take on an empty stomach at least 30 minutes before food. Disperse tablets by stirring in an appropriate amount of water, orange juice, or apple juice. (2.3)
- Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment by 50%. Avoid the use of Exjade in patients with severe (Child-Pugh C) hepatic impairment. (2.4)
- Reduce the starting dose by 50% in patients with renal impairment (ClCr 40–60 mL/min). (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets for oral suspension: 125 mg, 250 mg, 500 mg. (3)

----------CONTRAINDICATIONS----------

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min. (4)
- Patients with poor performance status. (4)
- Patients with high-risk myelodysplastic syndromes (MDS). (4)
- Patients with advanced malignancies. (4)
- Patients with platelet counts <50 x 10^9/L. (4)
- Known hypersensitivity to deferasirox or any component of Exjade. (4)

----------WARNINGS AND PRECAUTIONS----------

- Renal toxicity: Measure serum creatinine and creatinine clearance in duplicate before starting therapy. Monitor renal function during Exjade therapy and reduce dose or interrupt therapy for toxicity. (2.4, 5.1)
- Hepatic toxicity: Monitor hepatic function. Reduce dose or interrupt therapy for toxicity. (5.2)
- Fatal and nonfatal gastrointestinal bleeding, ulceration, and irritation: Risk may be greater in patients who are taking Exjade in combination with drugs that have known ulcerogenic or hemorrhagic potential. (5.3)
- Bone marrow suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during Exjade therapy. Interrupt therapy for toxicity. (5.4)
- Elderly: Monitor closely for toxicity due to the greater frequency of decreased hepatic, renal, and/or cardiac function. (5.5)
- Serious and severe hypersensitivity reactions: Discontinue Exjade and institute medical intervention. (5.6)
- Severe skin reactions including Stevens Johnson Syndrome: Discontinue Exjade. (5.7)

----------ADVERSE REACTIONS----------

In patients with transfusional iron overload, the most frequently occurring (>5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In Exjade-treated patients with NTDT syndromes, the most frequently occurring (>5%) adverse reactions are diarrhea, rash and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Avoid the use of Exjade with aluminum-containing antacid preparations. (7.1)
- Exjade increases the exposure of the CYP2C8 substrate repaglinide. Consider repaglinide dose reduction and monitor blood glucose levels. (7.3)
- Avoid the use of Exjade with CYP1A2 substrate theophylline. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2015

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FULL PRESCRIBING INFORMATION

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **Exjade can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.**
- **Measure serum creatinine and determine creatinine clearance in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)]*.**

Hepatic Failure

- **Exjade can cause hepatic injury including hepatic failure and death.**
- **Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter.**
- **Avoid use of Exjade in patients with severe (Child-Pugh C) hepatic impairment and reduce the dose in patients with moderate (Child Pugh B) hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.**

Gastrointestinal Hemorrhage

- **Exjade can cause gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts.**
- **Monitor patients and discontinue Exjade for suspected GI ulceration or hemorrhage *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

1.1 Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)

Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. This indication is based on a reduction of liver iron concentrations and serum ferritin levels *[see Clinical Studies (14)]*. An improvement in survival or disease-related symptoms has not been established *[see Indications and Usage (1.3)]*.

1.2 Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Exjade is indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw *[see Clinical Studies (14)]*. An improvement in survival or disease-related symptoms has not been established.

1.3 Limitation of Use

Controlled clinical trials of Exjade with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed *[see Clinical Studies (14)]*.

The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Transfusional Iron Overload

Exjade therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20

units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.

Prior to starting therapy, obtain:

- serum ferritin level
- baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method) *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*
- serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.9)]*

The recommended initial dose of Exjade for patients 2 years of age and older is 20 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.

After commencing therapy, monitor serum ferritin monthly and adjust the dose of Exjade, if necessary, every 3-6 months based on serum ferritin trends. Make dose adjustments in steps of 5 or 10 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 30 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 40 mg per kg may be considered. Doses above 40 mg per kg are not recommended.

If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with Exjade *[see Warnings and Precautions (5.10)]*.

2.2 Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Exjade therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.

Prior to starting therapy, obtain:

- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1 month apart *[see Clinical Studies (14)]*
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method) *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*
- Serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- Baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.9)]*

Initiating therapy:

- The recommended initial dose of Exjade is 10 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 20 mg/kg/day after 4 weeks.

During therapy:

- Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 20 mg/kg/day. Do not exceed a maximum of 20 mg/kg/day.
- If after 6 months of therapy, the LIC is 3–7 mg Fe/g dw, continue treatment with deferasirox at no more than 10 mg/kg/day.

- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, hepatic function, and renal function *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

2.3 Administration

Do not chew tablets or swallow them whole.

Take Exjade once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Completely disperse tablets by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Disperse doses of less than 1 g in 3.5 ounces of liquid and doses of 1 g or greater in 7 ounces of liquid. After swallowing the suspension, resuspend any residue in a small volume of liquid and swallow. Do not take Exjade with aluminum-containing antacid products *[see Drug Interactions (7.1)]*.

2.4 Use in Patients with Baseline Hepatic or Renal Impairment

Patients with Baseline Hepatic Impairment

Mild (Child-Pugh A) hepatic impairment: No dose adjustment is necessary.

Moderate (Child-Pugh B) hepatic impairment: Reduce the starting dose by 50%.

Severe (Child-Pugh C) hepatic impairment: Avoid Exjade *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.

Patients with Baseline Renal Impairment

For patients with renal impairment (ClCr 40–60 mL/min), reduce the starting dose by 50% *[see Use in Specific Populations (8.6)]*. Do not use Exjade in patients with serum creatinine greater than 2 times the upper limit of normal or creatinine clearance less than 40 mL/min *[see Contraindications (4)]*.

2.5 Dose Modifications for Increases in Serum Creatinine on Exjade

For serum creatinine increases while receiving Exjade *[see Warnings and Precautions (5.1)]* modify the dose as follows:

Transfusional Iron Overload

Adults and Adolescents (ages 16 years and older):

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, reduce the dose by 10 mg per kg.

Pediatric Patients (ages 2–15 years):

- Reduce the dose by 10 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

All Patients (regardless of age):

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min *[see Contraindications (4)]*.

Non-Transfusion-Dependent Thalassemia Syndromes

Adults and Adolescents (ages 16 years and older):

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, interrupt therapy if the dose is 5 mg per kg, or reduce by 50% if the dose is 10 or 20 mg per kg.

Pediatric Patients (ages 10–15 years):

- Reduce the dose by 5 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

All Patients (regardless of age):

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min *[see Contraindications (4)]*.

2.6 Dose Modifications Based on Concomitant Medications

UDP-glucuronosyltransferases (UGT) Inducers

Concomitant use of UGT inducers decreases Exjade systemic exposure. Avoid the concomitant use of potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) with Exjade. If you must administer Exjade with 1 of these agents, consider increasing the initial dose of Exjade by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.5)]*.

Bile Acid Sequestrants

Concomitant use of bile acid sequestrants decreases Exjade systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Exjade. If you must administer Exjade with 1 of these agents, consider increasing the initial dose of Exjade by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.6)]*.

3 DOSAGE FORMS AND STRENGTHS

- 125 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with “J” and “125” on one side and “NVR” on the other.
- 250 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with “J” and “250” on one side and “NVR” on the other.
- 500 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with “J” and “500” on one side and “NVR” on the other.

4 CONTRAINDICATIONS

Exjade is contraindicated in patients with:

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min *[see Warning and Precautions (5.1)];*
- Poor performance status;
- High-risk myelodysplastic syndromes;
- Advanced malignancies;
- Platelet counts <50 x 10^9/L;
- Known hypersensitivity to deferasirox or any component of Exjade *[see Warnings and Precautions (5.6), Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Toxicity, Renal Failure, and Proteinuria

Exjade can cause acute renal failure, fatal in some patients and requiring dialysis in others. Postmarketing experience showed that most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, Exjade-treated patients experienced dose-dependent increases in serum creatinine. In patients with transfusional iron overload, these increases in creatinine occurred at a greater frequency compared to deferoxamine-treated patients (38% versus 14%, respectively, in Study 1 and 36% versus 22%, respectively, in Study 3) *[see Adverse Reactions (6.1, 6.2)]*.

Measure serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (estimated by the Cockcroft-Gault method) before initiating therapy in all patients in order to establish a reliable pretreatment baseline. Monitor serum creatinine weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Monitor serum creatinine and/or creatinine clearance more frequently if creatinine levels are increasing. Dose reduction, interruption, or discontinuation based on increases in serum creatinine may be necessary *[see Dosage and Administration (2.5)]*.

Exjade is contraindicated in patients with creatinine clearance less than 40 mL/minute or serum creatinine greater than 2 times the age appropriate upper limit of normal.

Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with Exjade, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L.

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. In clinical trials in patients with transfusional iron overload, Exjade was temporarily withheld until the urine protein/creatinine ratio fell below 0.6 mg/mg. Monthly monitoring for proteinuria is recommended. The mechanism and clinical significance of the proteinuria are uncertain *[see Adverse Reactions (6.1)]*.

5.2 Hepatic Toxicity and Failure

Exjade can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) discontinued Exjade because of hepatic toxicity (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). Hepatic toxicity appears to be more common in patients greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure *[see Adverse Reactions (6.1)]*.

Measure transaminases (AST and ALT) and bilirubin in all patients before the initiation of treatment and every 2 weeks during the first month and at least monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.

Avoid the use of Exjade in patients with severe (Child-Pugh C) hepatic impairment. Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.7)]*. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.

5.3 Gastrointestinal (GI) Ulceration, Hemorrhage, and Perforation

GI hemorrhage, including deaths, has been reported, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Nonfatal upper GI irritation, ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Exjade *[see Adverse Reactions (6.1)]*. Monitor 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. The risk of gastrointestinal hemorrhage may be increased when administering Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome) *[see Adverse Reactions (6.2)]*.

5.4 Bone Marrow Suppression

Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events, have been reported in patients treated with Exjade. Preexisting hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with Exjade in patients who develop cytopenias until the cause of the cytopenia has been determined. Exjade is contraindicated in patients with platelet counts below 50 x 10^9/L.

5.5 Increased Risk of Toxicity in the Elderly

Exjade has been associated with serious and fatal adverse reactions in the postmarketing setting, predominantly in elderly patients. Monitor elderly patients treated with Exjade more frequently for toxicity *[see Use in Specific Populations (8.5)]*.

5.6 Hypersensitivity

Exjade may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment *[see Adverse Reactions (6.2)]*. If reactions are severe, discontinue Exjade and institute appropriate medical intervention. Exjade is contraindicated in patients with known hypersensitivity to Exjade.

5.7 Severe Skin Reactions

Severe skin reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme, have been reported during Exjade therapy *[see Adverse Reactions (6.2)]*. If SJS or erythema multiforme is suspected, discontinue Exjade immediately and do not reintroduce Exjade therapy.

5.8 Skin Rash

Rashes may occur during Exjade treatment *[see Adverse Reactions (6.1)]*. For rashes of mild to moderate severity, Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with Exjade. Reintroduction at a lower dose with escalation may be considered after resolution of the rash.

5.9 Auditory and Ocular Abnormalities

Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) were reported at a frequency of <1% with Exjade therapy in the clinical studies. Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting Exjade treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.

5.10 Overchelation

For patients with transfusional iron overload, measure serum ferritin monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500 mcg/L, consider interrupting therapy with Exjade, since overchelation may increase Exjade toxicity *[see Dosage and Administration (2.1)]*.

For patients with NTDT, measure LIC by liver biopsy or by using an FDA-cleared or approved method for monitoring patients receiving deferasirox therapy every 6 months on treatment. Interrupt Exjade administration when the LIC is less than 3 mg Fe/g dw. Measure serum ferritin monthly, and if the serum ferritin falls below 300 mcg/L, interrupt Exjade and obtain a confirmatory LIC *[see Clinical Studies (14)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed in other sections of the labeling:

- Renal Toxicity, Renal Failure, and Proteinuria *[see Warnings and Precautions (5.1)]*
- Hepatic Toxicity and Failure *[see Warnings and Precautions (5.2)]*

- Gastrointestinal (GI) Hemorrhage *[see Warnings and Precautions (5.3)]*
- Bone Marrow Suppression *[see Warnings and Precautions (5.4)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.7)]*
- Skin Rash *[see Warnings and Precautions (5.8)]*
- Auditory and Ocular Abnormalities *[see Warnings and Precautions (5.9)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Transfusional Iron Overload

A total of 700 adult and pediatric patients were treated with Exjade (deferasirox) for 48 weeks in premarketing studies. These included 469 patients with beta-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were <16 years of age. In the sickle cell disease population, 89% of patients were black. Median treatment duration among the sickle cell patients was 51 weeks. Of the 700 patients treated, 469 (403 beta-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 88-205 weeks.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. These studies varied in duration from 1 to 5 years. The discontinuation rate across studies in the first year was 46% (AEs 20%, withdrawal of consent 10%, death 8%, other 4%, lab abnormalities 3%, and lack of efficacy 1%). Among 47 patients enrolled in the study of 5-year duration, 10 remained on Exjade at the completion of the study.

Table 1 displays adverse reactions occurring in >5% of Exjade-treated beta-thalassemia patients (Study 1), sickle cell disease patients (Study 3), and patients with MDS (MDS pool). Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent adverse reactions reported with a suspected relationship to Exjade. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

Table 1. Adverse Reactions* Occurring in >5% of Exjade-treated Patients in Study 1, Study 3, and MDS Pool

	Study 1 (Beta-thalassemia)		**Study 3 (Sickle Cell Disease)**		**MDS Pool**
Preferred Term	**EXJADE N=296 n (%)**	**Deferoxamine N=290 n (%)**	**EXJADE N=132 n (%)**	**Deferoxamine N=63 n (%)**	**EXJADE N=627 n (%)**
Abdominal Pain**	63 (21)	41 (14)	37 (28)	9 (14)	145 (23)
Diarrhea	35 (12)	21 (7)	26 (20)	3 (5)	297 (47)
Creatinine Increased***	33 (11)	0 (0)	9 (7)	0	89 (14)
Nausea	31 (11)	14 (5)	30 (23)	7 (11)	161 (26)
Vomiting	30 (10)	28 (10)	28 (21)	10 (16)	83 (13)
Rash	25 (8)	9 (3)	14 (11)	3 (5)	83 (13)

*Adverse reaction frequencies are based on adverse events reported regardless of relationship to study drug.
**Includes ‘abdominal pain’, ‘abdominal pain lower’, and ‘abdominal pain upper’ which were reported as adverse events.
***Includes ‘blood creatinine increased’ and ‘blood creatinine abnormal’ which were reported as adverse events. Also see Table 2.

In Study 1, a total of 113 (38%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) and 25 (8%) patients required dose reductions. Increases in serum creatinine appeared to be dose related *[see Warnings and Precautions (5.1)]*. In this study, 17 (6%) patients treated with Exjade developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2

consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued Exjade therapy *[see Warnings and Precautions (5.2)]*. An additional 2 patients, who did not have elevations in SGPT/ALT >5 times the upper limit of normal, discontinued Exjade because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related. Adverse reactions that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In Study 3, a total of 48 (36%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) *[see Warnings and Precautions (5.1)]*. Of the patients who experienced creatinine increases in Study 3, 8 Exjade-treated patients required dose reductions. In this study, 5 patients in the Exjade group developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits and 1 patient subsequently had Exjade permanently discontinued. Four additional patients discontinued Exjade due to adverse reactions with a suspected relationship to study drug, including diarrhea, pancreatitis associated with gallstones, atypical tuberculosis, and skin rash.

In the MDS pool, in the first year, a total of 229 (37%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 consecutive occasions (Table 2) and 8 (3.5%) patients permanently discontinued *[see Warnings and Precautions (5.1)]*. A total of 5 (0.8%) patients developed SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits. The most frequent adverse reactions that led to discontinuation included increases in serum creatinine, diarrhea, nausea, rash, and vomiting. Death was reported in the first year in 52 (8%) of patients *[see Clinical Studies (14)]*.

Table 2. Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1, Study 3, and MDS Pool

	Study 1 (Beta-thalassemia)		**Study 3 (Sickle Cell Disease)**		**MDS Pool**
Laboratory Parameter	**EXJADE N=296 n (%)**	**Deferoxamine N=290 n (%)**	**EXJADE N=132 n (%)**	**Deferoxamine N=63 n (%)**	**EXJADE N=627 n (%)**
Serum Creatinine					
Creatinine increase >33% at 2 consecutive postbaseline visits	113 (38)	41 (14)	48 (36)	14 (22)	229 (37)
Creatinine increase >33% and >ULN at 2 consecutive postbaseline visits	7 (2)	1 (0)	3 (2)	2 (3)	126 (20)
SGPT/ALT					
SGPT/ALT >5 x ULN at 2 postbaseline visits	25 (8)	7 (2)	2 (2)	0	9 (1)
SGPT/ALT >5 x ULN at 2 consecutive postbaseline visits	17 (6)	5 (2)	5 (4)	0	5 (1)

Non-Transfusion-Dependent Thalassemia Syndromes

In Study 4, 110 patients with NTDT received 1 year of treatment with Exjade 5 or 10 mg/kg/day and 56 patients received placebo in a double-blind, randomized trial. In Study 5, 130 of the patients who completed Study 4 were treated with open-label Exjade at 5, 10, or 20 mg/kg/day (depending on the baseline LIC) for 1 year *[see Clinical Studies (14)]*. Table 3 displays adverse reactions occurring in >5% in any group. The most frequent adverse reactions with a suspected relationship to study drug were nausea, rash, and diarrhea.

Table 3. Adverse Reactions Occurring in >5% in NTDT Patients

	Study 4		Study 5
	EXJADE N=110 n (%)	**Placebo N=56 n (%)**	**EXJADE N=130 n (%)**
Any adverse reaction	**31 (28)**	**9 (16)**	**27 (21)**
Nausea	7 (6)	4 (7)	2 (2)
Rash	7 (6)	1 (2)	2 (2)
Diarrhea	5 (5)	1 (2)	7 (5)

In Study 4, 1 patient in the placebo 10 mg/kg/day group experienced an ALT increase to >5 times ULN and >2 times baseline (Table 4). Three Exjade-treated patients (all in the 10 mg/kg/day group) had 2 consecutive serum creatinine level increases >33% from baseline and >ULN. Serum creatinine returned to normal in all 3 patients (in 1 spontaneously and in the other 2 after drug interruption). Two additional cases of ALT increase and 2 additional cases of serum creatinine increase were observed in the 1-year extension of Study 4.

Table 4. Number (%) of NTDT Patients with Increases in Serum Creatinine or SGPT/ALT

	Study 4		Study 5
Laboratory Parameter	**EXJADE N=110 n (%)**	**Placebo N=56 n (%)**	**EXJADE N=130 n (%)**
Serum creatinine (>33% increase from baseline and >ULN at ≥2 consecutive postbaseline values)	3 (3)	0	2 (2)
SGPT/ALT (>5 x ULN and >2 x baseline)	1 (1)	1 (2)	2 (2)

Proteinuria

In clinical studies, urine protein was measured monthly. 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 *[see Warnings and Precautions (5.1)]*.

Other Adverse Reactions

In the population of more than 5,000 patients with transfusional iron overload who have been treated with Exjade during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract, hearing loss, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, and renal tubulopathy (Fanconi's Syndrome). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis, esophagitis, and erythema multiforme. Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

6.2 Postmarketing Experience

The following adverse reactions have been spontaneously reported during post-approval use of Exjade in the transfusional iron overload setting. 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.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), leukocytoclastic vasculitis, urticaria, alopecia

Immune system disorders: hypersensitivity reactions (including anaphylaxis and angioedema)

Renal and urinary disorders: renal tubular necrosis, acute renal failure, tubulointerstitial nephritis

Hepatobiliary disorders: hepatic failure

Gastrointestinal disorders: gastrointestinal hemorrhage, gastrointestinal perforation

Blood and lymphatic system disorders: worsening anemia

7 DRUG INTERACTIONS

7.1 Aluminum Containing Antacid Preparations

The concomitant administration of Exjade and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, avoid use of Exjade with aluminum-containing antacid preparations due to the mechanism of action of Exjade.

7.2 Agents Metabolized by CYP3A4

Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are coadministered. Closely monitor patients for signs of reduced effectiveness when deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil) *[see Clinical Pharmacology (12.3)]*.

7.3 Agents Metabolized by CYP2C8

Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are coadministered. If Exjade and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when Exjade is coadministered with other CYP2C8 substrates *[see Clinical Pharmacology (12.3)]*.

7.4 Agents Metabolized by CYP1A2

Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are coadministered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with Exjade. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with Exjade. Closely monitor patients for signs of exposure related toxicity when Exjade is coadministered with other drugs metabolized by CYP1A2 *[see Clinical Pharmacology (12.3)]*.

7.5 Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism

Deferasirox is a substrate of UGT1A1 and to a lesser extent UGT1A3. The concomitant use of Exjade with potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade efficacy due to a possible decrease in deferasirox concentration. Avoid the concomitant use of potent UGT inducers with Exjade. Consider increasing the initial dose of Exjade if you must coadminister these agents together *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

7.6 Bile Acid Sequestrants

Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Exjade due to a possible decrease in deferasirox concentration. If you must coadminister these agents together, consider increasing the initial dose of Exjade *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with Exjade in pregnant women. Administration of deferasirox to animals during pregnancy and lactation resulted in decreased offspring viability and an increase in renal anomalies in male offspring at exposures that were less than the recommended human exposure. Exjade should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryofetal developmental studies, pregnant rats and rabbits received oral deferasirox during the period of organogenesis at doses up to (100 mg per kg/day in rats and 50 mg per kg/day in rabbits) 0.8 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. These doses resulted in maternal toxicity but no fetal harm was observed.

In a prenatal and postnatal developmental study, pregnant rats received oral deferasirox daily from organogenesis through lactation day 20 at doses (10, 30, and 90 mg per kg/day) 0.08, 0.2, and 0.7 times the MRHD on a mg/m^2 basis. Maternal toxicity, loss of litters, and decreased offspring viability occurred at 0.7 times the MRHD on a mg/m^2 basis, and increases in renal anomalies in male offspring occurred at 0.2 times the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

It is not known whether Exjade is excreted in human milk. Deferasirox and its metabolites were excreted in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from deferasirox and its metabolites, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Of the 700 patients with transfusional iron overload who received Exjade during clinical studies, 292 were pediatric patients 2-<16 years of age with various congenital and acquired anemias, including 52 patients age 2-<6 years, 121 patients age 6-<12 years and 119 patients age 12-<16 years. Seventy percent of these patients had beta-thalassemia. Children between the ages of 2-<6 years have a systemic exposure to Exjade approximately 50% of that of adults *[see Clinical Pharmacology (12.3)]*. However, the safety and efficacy of Exjade in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults *[see Clinical Studies (14), Indications and Usage (1), Dosage and Administration (2.1)]*.

Growth and development in patients with chronic iron overload due to blood transfusions were within normal limits in children followed for up to 5 years in clinical trials.

Sixteen pediatric patients (10 to <16 years of age) with chronic iron overload and NTDT were treated with Exjade in clinical studies. The safety and efficacy of Exjade in these children was similar to that seen in the adults. The recommended starting dose and dosing modification are the same for children and adults with chronic iron overload in NTDT *[see Clinical Studies (14), Indications and Usage (1.2), Dosage and Administration (2.2)]*.

Safety and effectiveness have not been established in pediatric patients with chronic iron overload due to blood transfusions who are less than 2 years of age or pediatric patients with chronic iron overload and NTDT who are less than 10 years of age.

8.5 Geriatric Use

Four hundred thirty-one (431) patients ≥65 years of age were studied in clinical trials of Exjade in the transfusional iron overload setting. The majority of these patients had myelodysplastic syndrome (MDS) (n=393). In these trials, elderly patients experienced a higher frequency of adverse reactions than younger patients. Monitor elderly patients for early signs or symptoms of adverse reactions that may require a

dose adjustment. Elderly patients are at increased risk for toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

8.6 Renal Impairment

For patients with renal impairment (ClCr 40–60 mL/min), reduce the starting dose by 50% *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*. Exjade is contraindicated in patients with a creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal *[see Contraindications (4)]*.

Exjade can cause renal failure. Monitor serum creatinine and calculate creatinine clearance (using Cockcroft-Gault method) during treatment in all patients. Reduce, interrupt or discontinue Exjade dosing based on increases in serum creatinine *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)]*.

8.7 Hepatic Impairment

In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC of deferasirox increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

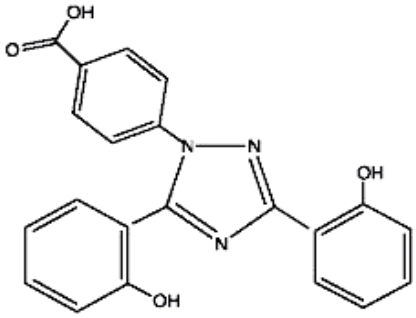
Avoid the use of Exjade in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, the starting dose should be reduced by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.

10 OVERDOSAGE

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In 1 case, this resulted in hepatitis which resolved without long-term consequences after a dose interruption. Single doses up to 80 mg per kg per day in iron overloaded beta-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy volunteers, single doses of up to 40 mg per kg per day were tolerated. There is no specific antidote for Exjade. In case of overdose, induce vomiting and employ gastric lavage.

11 DESCRIPTION

Exjade (deferasirox) is an iron chelating agent. Exjade tablets for oral suspension contain 125 mg, 250 mg, or 500 mg deferasirox. Deferasirox is designated chemically as 4-[3,5-Bis (2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid and its structural formula is:



Deferasirox is a white to slightly yellow powder. Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4.

Inactive Ingredients: Lactose monohydrate (NF), crospovidone (NF), povidone (K30) (NF), sodium lauryl sulphate (NF), microcrystalline cellulose (NF), silicon dioxide (NF), and magnesium stearate (NF).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Exjade (deferasirox) is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

12.2 Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study showed that deferasirox (10, 20, and 40 mg per kg per day) was able to induce a mean net iron excretion (0.119, 0.329, and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1-0.5 mg per kg per day). Iron excretion was predominantly fecal.

12.3 Pharmacokinetics

Absorption

Exjade is absorbed following oral administration with median times to maximum plasma concentration (t_{max}) of about 1.5-4 hours. The C_{max} and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3-2.3 after multiple doses. The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (AUC) of deferasirox was variably increased when taken with a meal.

Distribution

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (V_{ss}) of deferasirox is 14.37 ± 2.69 L in adults.

Metabolism

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy volunteer study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) by interfering with the enterohepatic recycling of deferasirox.

Excretion

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8-16 hours following oral administration.

Drug Interactions

Midazolam: In healthy volunteers, the concomitant administration of Exjade and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam peak concentration by 23% and exposure by 17%. In the clinical setting, this effect may be more pronounced. The study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox *[see Drug Interactions (7.2)]*.

Repaglinide: In a healthy volunteer study, the concomitant administration of Exjade (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold of control and an increase in C_{max} of 62% *[see Drug Interactions (7.3)]*.

Theophylline: In a healthy volunteer study, the concomitant administration of Exjade (repeated dose of 30 mg per kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an approximate doubling of the theophylline AUC and elimination half-life. The single dose C_{max} was not affected, but an increase in theophylline C_{max} is expected to occur with chronic dosing *[see Drug Interactions (7.4)]*.

Rifampicin: In a healthy volunteer study, the concomitant administration of Exjade (single dose of 30 mg per kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (600 mg/day for 9 days) resulted in a decrease of deferasirox systemic exposure (AUC) by 44% *[see Drug Interactions (7.5)]*.

Cholestyramine: The concomitant use of Exjade with bile acid sequestrants may result in a decrease in Exjade efficacy. In healthy volunteers, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) *[see Drug Interactions (7.6)]*.

In vitro studies:

- Cytochrome P450 Enzymes: Deferasirox inhibits human CYP3A4, CYP2C8, CYP1A2, CYP2A6, CYP2D6, and CYP2C19 *in vitro*.
- Transporter Systems: The addition of cyclosporin A (PgP/MRP1/MRP2 inhibitor) or verapamil (PgP/MRP1 inhibitor) did not influence ICL670 permeability *in vitro*.

Pharmacokinetics in Specific Populations

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children <6 years of age, systemic exposure was about 50% lower than in adults.

Geriatric: The pharmacokinetics of deferasirox have not been studied in elderly patients (65 years of age or older).

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

Renal Impairment: Compared to patients with MDS and ClCr >60 mL/min, patients with MDS and ClCr 40 to 60 mL/min (n=34) had approximately 50% higher mean deferasirox trough plasma concentrations.

12.6 QT Prolongation

The effect of 20 and 40 mg per kg per day of deferasirox on the QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female volunteers age 18-65 years. No evidence of prolongation of the QTc interval was observed in this study.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg per kg per day (0.48 times the MRHD on a mg/m^2 basis). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg per kg per day (0.81 times the MRHD on a mg/m^2 basis) in males and 300 mg per kg per day (1.21 times the MRHD on a mg/m^2 basis) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg per kg per day (0.6 times the MRHD on a mg/m^2 basis) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Transfusional Iron Overload

The primary efficacy study, Study 1, was a multicenter, open-label, randomized, active-comparator control study to compare Exjade (deferasirox) and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral Exjade at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous Desferal (deferoxamine) at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2-3, >3-7, >7-14, and >14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

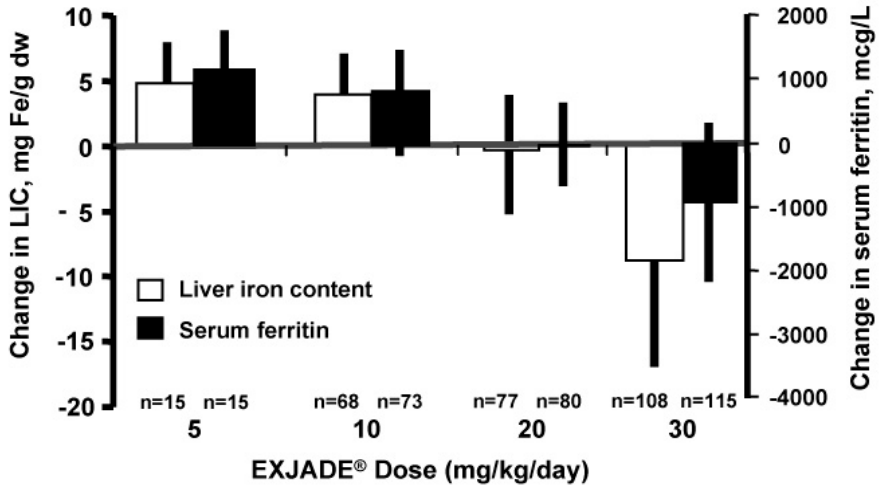
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of ≥3 mg Fe/g dry weight for baseline values ≥10 mg Fe/g dry weight, reduction of baseline values between 7 and <10 to <7 mg Fe/g dry weight, or maintenance or reduction for baseline values <7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with Exjade and 290 with deferoxamine. The mean age was 17.1 years (range, 2-53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (Exjade n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse event. The percentage of patients achieving the primary endpoint was 52.9% for Exjade and 66.4% for deferoxamine. The relative efficacy of Exjade to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with Exjade and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with Exjade doses of 20 to 30 mg per kg per day. Exjade doses below 20 mg per kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg per kg per day is recommended *[see Dosage and Administration (2.1)]*.

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following EXJADE (5-30 mg per kg per day) in Study 1



Study 2 was an open-label, noncomparative trial of efficacy and safety of Exjade given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg per kg per day of Exjade based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other,

n=22). 19% of patients were <16 years of age and 16% were ≥65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 was a multicenter, open-label, randomized trial of the safety and efficacy of Exjade relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to Exjade at doses of 5, 10, 20, or 30 mg per kg per day or subcutaneous deferoxamine at doses of 20-60 mg per kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with Exjade and 63 with deferoxamine. 44% of patients were <16 years of age and 91% were black. At end of study, the mean change in LIC (as measured by magnetic susceptometry by a superconducting quantum interference device) in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving Exjade (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

One-hundred five (105) patients with thalassemia major and cardiac iron overload were enrolled in a study assessing the change in cardiac MRI T2* value (measured in milliseconds, ms) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to <20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of Exjade therapy increased from 11.98 ms at baseline to 17.12 ms at 3 years. Cardiac T2* values improved in patients with severe cardiac iron overload (<10 ms) and in those with mild to moderate cardiac iron overload (≥10 to <20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. Two hundred thirty-nine of the 627 patients were enrolled in trials that limited enrollment to patients with IPSS Low or Intermediate 1 risk MDS and the remaining 388 patients were enrolled in trials that did not specify MDS risk stratification but required a life expectancy of greater than 1 year. Planned duration of treatment in these trials ranged from 1 year (365 patients) to 5 years (47 patients). These trials evaluated the effects of Exjade therapy on parameters of iron overload, including LIC (125 patients) and serum ferritin (627 patients). Percent of patients completing planned duration of treatment was 51% in the largest 1 year study, 52% in the 3-year study and 22% in the 5 year study. The major causes for treatment discontinuation were withdrawal of consent, adverse reaction, and death. Over 1 year of follow-up across these pooled studies, mean change in serum ferritin was -332.8 (±2615.59) mcg/L (n=593) and mean change in LIC was -5.9 (±8.32) mg Fe/g dw (n=68). Results of these pooled studies in 627 patients with MDS suggest a progressive decrease in serum ferritin and LIC beyond 1 year in those patients who are able to continue Exjade. No controlled trials have been performed to demonstrate that these reductions improve morbidity or mortality in patients with MDS. Adverse reactions with Exjade therapy occur more frequently in older patients *[see Use in Specific Populations (8.5)]*. In elderly patients, including those with MDS, individualize the decision to remove accumulated iron based on clinical circumstances and the anticipated clinical benefit and risks of Exjade therapy.

Non-Transfusion Dependent Thalassemia

Study 4 was a randomized, double-blind, placebo-controlled trial of treatment with Exjade for patients 10 years of age or older with NTDT syndromes and iron overload. Eligible patients had an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin exceeding 300 mcg/L at screening (2 consecutive values at least 14 days apart from each other). A total of 166 patients were randomized, 55 to the Exjade 5 mg/kg/day dose group, 55 to the Exjade 10 mg/kg/day dose group, and 56 to placebo (28 to each matching placebo group). Doses could be increased after 6 months if the LIC exceeded 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The patients enrolled included 89 males and 77 females. The underlying disease was beta-thalassemia intermedia in 95 (57%) patients, HbE beta-thalassemia in 49 (30%) patients, and alpha-thalassemia in 22 (13%) patients. There were 17 pediatric patients in the study. Caucasians comprised 57% of the study population and Asians comprised 42%. The median baseline LIC (range) for all patients was 12.1 (2.6-49.1) mg Fe/g dw. Follow-up was for 1 year. The primary efficacy endpoint of change in LIC from baseline to Week 52 was statistically significant in favor of both Exjade dose groups compared with placebo ($p \leq 0.001$) (Table 5). Furthermore, a statistically significant dose effect of Exjade was observed in favor of the 10 mg/kg/day dose group (10 versus 5 mg/kg/day, $p=0.009$). In a descriptive analysis, the target LIC (less than 5 mg Fe/g dw) was

reached by 15 (27%) of 55 patients in the 10 mg/kg/day arm, 8 (15%) of 55 patients in the 5 mg/kg/day arm and 2 (4%) of 56 patients in the combined placebo groups.

Table 5. Absolute Change in LIC at Week 52 in NTDT Patients

	Starting Dose[1]			
	Placebo	**EXJADE 5 mg/kg/day**	**EXJADE 10 mg/kg/day**	**EXJADE 20 mg/kg/day**
Study 4[2]				
Number of Patients	n=54	n=51	n=54	-
Mean LIC at Baseline (mg Fe/g dw)	16.1	13.4	14.4	-
Mean Change (mg Fe/g dw)	+0.4	-2.0	-3.8	-
(95% Confidence Interval)	(-0.6, +1.3)	(-2.9, -1.0)	(-4.8, -2.9)	-
Study 5				
Number of Patients	-	n=8	n=77	n=43
Mean LIC at Baseline (mg Fe/g dw)	-	5.6	8.8	23.5
Mean Change (mg Fe/g dw)	-	-1.5	-2.8	-9.1
(95% Confidence Interval)	-	(-3.7, +0.7)	(-3.4, -2.2)	(-11.0, -7.3)

[1]Randomized dose in Study 4 or assigned starting dose in Study 5

[2]Least square mean change for Study 4

Study 5 was an open-label trial of Exjade for the treatment of patients previously enrolled on Study 4, including cross-over to active treatment for those previously treated with placebo. The starting dose of Exjade in Study 5 was assigned based on the patient's LIC at completion of Study 4, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3-15 mg Fe/g dw, and observation if the LIC was less than 3 mg Fe/g dw. Patients could continue on 5 mg/kg/day if they had previously exhibited at least a 30% reduction in LIC. Doses could be increased to a maximum of 20 mg/kg/day after 6 months if the LIC was more than 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The primary efficacy endpoint in Study 5 was the proportion of patients achieving an LIC less than 5 mg Fe/g dw. A total of 133 patients were enrolled. Twenty patients began Study 5 with an LIC less than 5 mg Fe/g dw. Of the 113 patients with a baseline LIC of at least 5 mg Fe/g dw in Study 5, the target LIC (less than 5 mg Fe/g dw) was reached by 39 (35%). The responders included 4 (10%) of 39 patients treated at 20 mg/kg/day for a baseline LIC exceeding 15 mg Fe/g dw, and 31 (51%) of 61 patients treated at 10 mg/kg/day for a baseline LIC between 5 and 15 mg Fe/g dw. The absolute change in LIC at Week 52 by starting dose is shown in Table 5 above.

16 HOW SUPPLIED/STORAGE AND HANDLING

Exjade is provided as 125 mg, 250 mg, and 500 mg tablets for oral suspension.

125 mg

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "125" on one side and "NVR" on the other.

Bottles of 30 tablets……..(NDC 0078-0468-15)

250 mg

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "250" on one side and "NVR" on the other.

Bottles of 30 tablets……..(NDC 0078-0469-15)

500 mg

Off-white, round, flat tablet with beveled edge and imprinted with “J” and “500” on one side and “NVR” on the other.

Bottles of 30 tablets……..(NDC 0078-0470-15)

Store Exjade tablets at 25°C (77°F); excursions are permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

- Advise patients to take Exjade once daily on an empty stomach at least 30 minutes prior to food, preferably at the same time every day. Instruct patients to completely disperse the tablets in water, orange juice, or apple juice, and drink the resulting suspension immediately. After the suspension has been swallowed, resuspend any residue in a small volume of the liquid and swallow *[see Dosage and Administration (2.3)]*.

- Advise patients not to chew tablets or swallow them whole *[see Dosage and Administration (2.3)]*.

- Caution patients not to take aluminum-containing antacids and Exjade simultaneously *[see Drug Interactions (7.1)]*.
- Because auditory and ocular disturbances have been reported with Exjade, conduct auditory testing and ophthalmic testing before starting Exjade treatment and thereafter at regular intervals *[see Warnings and Precautions (5.9)]*.

- Caution patients experiencing dizziness to avoid driving or operating machinery *[see Adverse Reactions (6.1)]*.

- Caution patients about the potential for the development of GI ulcers or bleeding when taking Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants *[see Warnings and Precautions (5.3)]*.

- Caution patients about potential loss of effectiveness of drugs metabolized by CYP3A4 (e.g., cyclosporine, simvastatin, hormonal contraceptive agents) when Exjade is administered with these drugs *[see Drug Interactions (7.2)]*.

- Caution patients about potential loss of effectiveness of Exjade when administered with drugs that are potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). Based on serum ferritin levels and clinical response, consider increases in the dose of Exjade when concomitantly used with potent UGT inducers *[see Drug Interactions (7.5)]*.

- Caution patients about potential loss of effectiveness of Exjade when administered with drugs that are bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol). Based on serum ferritin levels and clinical response, consider increases in the dose of Exjade when concomitantly used with bile acid sequestrants *[see Drug Interactions (7.6)]*.

- Perform careful monitoring of glucose levels when repaglinide is used concomitantly with Exjade. An interaction between Exjade and other CYP2C8 substrates like paclitaxel cannot be excluded *[see Drug Interactions (7.3)]*.

- Advise patients that blood tests will be performed because Exjade may affect your kidneys, liver, or blood cells. The blood tests will be performed every month or more frequently if you are at increased risk of complications (e.g., preexisting kidney condition, are elderly, have multiple medical conditions, or are taking medicine that affects your organs). There have been reports of severe kidney and liver problems, blood disorders, stomach hemorrhage and death in patients taking Exjade *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)]*.

- Skin rashes may occur during Exjade treatment and if severe, interrupt treatment. Serious allergic reactions (which include swelling of the throat) have been reported in patients taking Exjade, usually within the

first month of treatment. If reactions are severe, advise patients to stop taking Exjade and contact their doctor immediately *[see Warnings and Precautions (5.6, 5.7, 5.8)]*.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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T201X-XX
Month Year