NOVARTIS

Deferasirox

Jadenu®

90 mg, 180 mg and 360 mg Film-coated Tablets

Iron chelating agent

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

90 mg Film-coated tablet: Light blue colored, unscored, ovaloid, biconvex film-coated tablet with beveled edges with "NVR" on one side and "90" on a slight upward slope in between two debossed curved lines on the other side

180 mg Film-coated tablet: Medium blue colored, unscored, ovaloid, biconvex film-coated tablet with beveled edges with "NVR" on one side and "180" on a slight upward slope in between two debossed curved lines on the other side

360 mg Film-coated tablet: Dark blue colored, unscored, ovaloid, biconvex film-coated tablet with beveled edges with "NVR" on one side and "360" on a slight upward slope in between two debossed curved lines on the other side

Active substance(s)

Each film-coated tablet contains 90 mg / 180 mg / 360 mg deferasirox as active substance.

Certain dosage strengths may not be available in all countries.

Excipients

Microcrystalline cellulose; crospovidone; povidone (K30); magnesium stearate; colloidal silicon dioxide; poloxamer 188; coating material: hypromellose; titanium dioxide (E171); polyethylene glycol (4000); talc; FD&C blue #2/Indigo carminine aluminum lake (E132).

INDICATIONS

Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).

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/mL.

DOSAGE AND ADMINISTRATION

Transfusional iron overload

DEFERASIROX (JADENU®) 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 1,000 mcg/L.

Prior to starting therapy, obtain:

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

The recommended initial dose of DEFERASIROX (JADENU®) for patients 2 years of age and older is 14 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet or nearest whole sachet content for granules. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

After commencing therapy, monitor serum ferritin monthly and adjust the dose of DEFERASIROX (JADENU®), if necessary, every 3 to 6 months based on serum ferritin trends. Make dose adjustments in steps of 3.5 or 7 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 21 mg per kg (e.g., serum ferritin levels persistently above 2,500 mcg/L and not showing a decreasing trend over time), doses of up to 28 mg per kg may be considered. Doses above 28 mg per kg are not recommended.

If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with DEFERASIROX (JADENU®) to minimize the risk of overchelation *[see Warnings and Precautions].*

Non-transfusion-dependent thalassemia (NTDT) syndromes

DEFERASIROX (JADENU®) 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]*
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the CLcr (Cockcroft-Gault method) *[see Dosage and Administration,*

Warnings and Precautions]

- Serum transaminases and bilirubin *[see Dosage and Administration, Warnings and Precautions]*
- Baseline auditory and ophthalmic examinations *[see Warnings and Precautions]*

Initiating therapy:

- The recommended initial dose of DEFERASIROX (JADENU®) is 7 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet or nearest whole sachet content for granules.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 14 mg/kg/day after 4 weeks.

During therapy:

- Monitor serum ferritin monthly to assess the patient's response to therapy and to minimize the risk of overchelation *[see section Warnings and Precautions]*. 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 14 mg/kg/day. Do not exceed a maximum of 14 mg/kg/day.
- If after 6 months of therapy, the LIC is 3 to 7 mg Fe/g dw, continue treatment with deferasirox at no more than 7 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]*.

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

Special populations

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 DEFERASIROX (JADENU®) tablets *[see Warnings and Precautions, Use in Specific Populations]*.

Patients with Baseline Renal Impairment

For patients with CLcr 40 to 60 mL/min, reduce the starting dose by 50% *[see Use in Specific Populations]*. Do not use DEFERASIROX (JADENU®) in patients with serum creatinine greater than two times the age-appropriate upper limit of normal (ULN) or CLcr less than 40 mL/min *[see Contraindications]*.

Dose Modifications for Increase in Serum Creatinine

For serum creatinine increases while receiving DEFERASIROX (JADENU®) *[see Warnings and Precautions]* 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 7 mg per kg.

Pediatric Patients (ages 2 to 15 years):

- Reduce the dose by 7 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 (ULN).

All Patients (regardless of age):

- Discontinue therapy for serum creatinine greater than two times the age-appropriate ULN or for creatinine clearance less than 40 mL/min. *[see Contraindications]*

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 3.5 mg per kg, or reduce by 50% if the dose is 7 or 14 mg per kg.

Pediatric Patients (ages 10 to 15 years):

- Reduce the dose by 3.5 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate ULN.

All Patients (regardless of age):

Discontinue therapy for serum creatinine greater than 2 times the age-appropriate ULN or for creatinine clearance less than 40 mL/min *[see Contraindications]*.

Method of administration

Swallow DEFERASIROX (JADENU®) tablets once daily with water or other liquids, preferably at the same time each day. Take DEFERASIROX (JADENU®) tablets on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/ lettuce, tomato, and 1 packet mustard). Do not take DEFERASIROX (JADENU®) tablets with aluminum-containing antacid products *[see Drug Interactions]*. For patients who

have difficulty swallowing whole tablets, DEFERASIROX (JADENU®) tablets may be crushed and mixed with soft foods (e.g., yogurt or apple sauce) immediately prior to use and administered orally. Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed and not stored for future use.

For patients who are currently on chelation therapy with Exjade tablets for oral suspension and converting to DEFERASIROX (JADENU®), the dose should be about 30% lower, rounded to the nearest whole tablet. The table below provides additional information on dosing conversion to DEFERASIROX (JADENU®).

	DEFERASIROX (EXJADE®) Tablets for oral suspension (white round tablet)	**DEFERASIROX (JADENU®) Tablets (film coated blue oval tablet)**
Transfusion-Dependent Iron Overload		
Starting Dose	20 mg/kg/day	14 mg/kg/day
Titration Increments	5–10 mg/kg	3.5–7 mg/kg
Maximum Dose	40 mg/kg/day	28 mg/kg/day
Non-Transfusion-Dependent Thalassemia Syndromes		
Starting Dose	10 mg/kg/day	7 mg/kg/day
Titration Increments	5–10 mg/kg	3.5–7 mg/kg
Maximum Dose	20 mg/kg/day	14 mg/kg/day

CONTRAINDICATIONS

Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal.

High risk myelodysplastic syndrome (MDS) patients and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Renal Toxicity, Renal Failure, and Proteinuria

DEFERASIROX (JADENU®) 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, deferasirox-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]*.

Measure serum creatinine in duplicate (due to variations in measurements) and determine the CLcr (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 CLcr 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]*.

DEFERASIROX (JADENU®) is contraindicated in patients with CLcr less than 40 mL/minute or serum creatinine greater than 2 times the age appropriate ULN.

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

Dose reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated.

Intermittent proteinuria (urine protein/creatinine ratio greater than 0.6 mg/mg) occurred in 18.6% of deferasirox-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. In clinical trials in patients with transfusional iron overload, deferasirox 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]*.

Hepatic Toxicity and Failure

Deferasirox can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) discontinued deferasirox 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]*.

Measure transaminases [aspartate transaminase (AST) and alanine transaminase (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 DEFERASIROX (JADENU®) 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, Use in Specific Populations]*. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.

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 deferasirox *[see Adverse Reactions]*. Monitor for signs and symptoms of GI

ulceration and hemorrhage during DEFERASIROX (JADENU®) therapy and promptly initiate additional evaluation and treatment if a serious GI adverse reaction is suspected. The risk of GI hemorrhage may be increased when administering DEFERASIROX (JADENU®) 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 GI perforation (including fatal outcome) *[see Adverse Reactions]*.

Bone Marrow Suppression

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

Increased Risk of Toxicity in the Elderly

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

Hypersensitivity

DEFERASIROX (JADENU®) 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]*. If reactions are severe, discontinue DEFERASIROX (JADENU®) and institute appropriate medical intervention. DEFERASIROX (JADENU®) is contraindicated in patients with known hypersensitivity to deferasirox products and should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox products due to the risk of anaphylactic shock.

Severe Skin Reactions

Severe skin reactions, including Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme, have been reported during deferasirox therapy *[see Adverse Reactions]*. The risk of other skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If sever skin reactions are suspected, discontinue DEFERASIROX (JADENU®) immediately and do not reintroduce DEFERASIROX (JADENU®) therapy.

Skin Rash

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

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 less than 1% with deferasirox therapy in the clinical studies. Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting DEFERASIROX (JADENU®) treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.

Overchelation

For patients with transfusional iron overload, measure serum ferritin monthly to assess the patient's response to therapy and minimize the risk of overchelation . If the serum ferritin falls below 500 mcg/L, consider interrupting therapy with DEFERASIROX (JADENU®), since overchelation may increase DEFERASIROX (JADENU®) toxicity *[see Dosage and Administration]*.

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 DEFERASIROX (JADENU®) 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 DEFERASIROX (JADENU®) and obtain a confirmatory LIC *[see Clinical Studies]*.

ADVERSE REACTIONS

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

- Renal Toxicity, Renal Failure, and Proteinuria *[see Warnings and Precautions)]*
- Hepatic Toxicity and Failure *[see Warnings and Precautions]*
- GI Hemorrhage *[see Warnings and Precautions]*
- Bone Marrow Suppression *[see Warnings and Precautions]*
- Hypersensitivity *[see Warnings and Precautions]*
- Severe Skin Reactions *[see Warnings and Precautions]*
- Skin Rash *[see Warnings and Precautions)]*
- Auditory and Ocular Abnormalities *[see Warnings and Precautions]*

Clinical Trials Experience

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. DEFERASIROX (JADENU®) was evaluated in healthy volunteer trials. Currently, there are no clinical data in patients with DEFERASIROX (JADENU®) tablets. DEFERASIROX (JADENU®) contains the same active ingredient as Exjade (deferasirox) tablets for oral suspension. The following adverse reactions have been reported with Exjade tablets for oral suspension.

Transfusional Iron Overload

A total of 700 adult and pediatric patients were treated with 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 less than 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 to 205 weeks.

Six hundred twenty-seven (627) patients with myelodysplastic syndrome (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% (Adverse Events (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 deferasirox at the completion of the study.

Table 1 displays adverse reactions occurring in greater than 5% of deferasirox-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 deferasirox. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

Table 1. Adverse Reactions[a] Occurring in >5% of Deferasirox-treated Patients in Study 1, Study 3, and MDS Pool

	Study 1 (Beta-thalassemia)		**Study 3 (Sickle Cell Disease)**		**MDS Pool**
Preferred Term	**Deferasirox N=296 n (%)**	**Deferoxamine N=290 n (%)**	**Deferasirox N=132 n (%)**	**Deferoxamine N=63 n (%)**	**Deferasirox N=627 n (%)**
Abdominal Pain[b]	63 (21)	41 (14)	37 (28)	9 (14)	145 (23)
Diarrhea	35 (12)	21 (7)	26 (20)	3 (5)	297 (47)
Creatinine Increased[c]	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)

Abbreviation: MDS, myelodysplastic syndrome.

[a]Adverse reaction frequencies are based on AEs reported regardless of relationship to study drug.

[b]Includes 'abdominal pain', 'abdominal pain lower', and 'abdominal pain upper'.

[c]Includes 'blood creatinine increased' and 'blood creatinine abnormal'. See also Table 2.

In Study 1, a total of 113 (38%) patients treated with deferasirox had increases in serum creatinine greater than 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]*. In this study, 17 (6%) patients treated with deferasirox developed elevations in serum glutamic-pyruvic transaminase (SGPT)/ALT levels greater than 5 times the upper limit of normal (ULN) at 2 consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued deferasirox therapy *[see Warnings and Precautions]*. An additional 2 patients, who did not have elevations in SGPT/ALT greater than 5 times the ULN, discontinued deferasirox 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 deferasirox had increases in serum creatinine greater than 33% above baseline on 2 separate occasions (Table 2) *[see Warnings and Precautions]*. Of the patients who experienced creatinine increases in Study 3, 8 deferasirox-treated patients required dose reductions. In this study, 5 patients in the deferasirox group developed elevations in SGPT/ALT levels greater than 5 times the ULN at 2 consecutive visits and 1 patient subsequently had deferasirox permanently discontinued. Four additional patients discontinued 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 deferasirox had increases in serum creatinine greater than 33% above baseline on 2 consecutive occasions (Table 2) and 8 (3.5%) patients permanently discontinued *[see Warnings and Precautions]*. A total of 5 (0.8%) patients developed SGPT/ALT levels greater than 5 times the ULN 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]*.

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	**Deferasirox N=296 n (%)**	**Deferoxamine N=290 n (%)**	**Deferasirox N=132 n (%)**	**Deferoxamine N=63 n (%)**	**Deferasirox N=627 n (%)**
Serum Creatinine					
Creatinine increase >33% at 2 postbaseline visits	113 (38)	41 (14)	48 (36)	14 (22)	229 (37)
Creatinine increase >33% and >ULN 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)

Abbreviations: ALT, alanine transaminase; MDS, myelodysplastic syndrome; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal.

Non-Transfusion-Dependent Thalassemia Syndromes

In Study 5, 110 patients with NTDT received 1 year of treatment with deferasirox 5 or 10 mg/kg/day and 56 patients received placebo in a double-blind, randomized trial. In Study 6, 130 of the patients who completed Study 5 were treated with open-label deferasirox at 5, 10, or 20 mg/kg/day (depending on the baseline LIC) for 1 year *[see Clinical Studies]*. In Study 7, 134 patients with NTDT of 10 years of age or older with iron overload, received deferasirox tablets for oral suspension for up to 5 years, at a starting dose of 10 mg/kg/day followed by dose adjustment at Week4, and then approximately every 6 months thereafter based on LIC levels. Table 3 and 4 display the frequency of adverse reactions in patients with NTDT. Adverse reactions with a suspected relationship to study drug were included in Table 3 if they occurred at ≥ 5% of patients in Study 5.

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

	Study 5		Study 6	Study 7
Any adverse reaction	**Deferasirox N=110 n (%)**	**Placebo N=56 n (%)**	**Deferasirox N=130 n (%)**	**Deferasirox N = 134 n (%)**
	31 (28)	**9 (16)**	**27 (21)**	**50 (37)**
Nausea	7 (6)	4 (7)	2 (2)[a]	7 (5)
Rash	7 (6)	1 (2)	2 (2)[a]	3 (2)[a]
Diarrhea	5 (5)	1 (2)	7 (5)	8 (6)

Abbreviation: NTDT, non-transfusion-dependent thalassemia.

[a] The occurrence of nausea, and rash are included for Study 6 and rash for Study 7 for consistency. There were no additional adverse reactions with a suspected relationship to study drug occurring in >5% of patients in Study 6 and Study 7.

In Study 5, 1 patient in the placebo 10 mg/kg/day group experienced an ALT increase to greater than 5 times ULN and greater than 2 times baseline (Table 4). Three deferasirox-treated patients (all in the 10 mg/kg/day group) had 2 consecutive serum creatinine level increases greater than 33% from baseline and greater than 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 5. The number (%) of patients with NTDT with increase in serum creatinine or SGPT/ALT in Study 5, Study 6, and Study 7 are presented in Table 4 below

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

Laboratory Parameter	**Study 5**		**Study 6**	**Study 7**
	Deferasirox N=110 n (%)	**Placebo N=56 n (%)**	**Deferasirox N=130 n (%)**	**Deferasirox N = 134 n (%)**

Serum creatinine (>33% increase from baseline and >ULN at ≥2 consecutive post baseline values)	3 (3)	0	2 (2)	2 (2)
SGPT/ALT (>5 x ULN and >2 x baseline)	1 (1)	1 (2)	2 (2)	1 (1)
Abbreviations: ALT, alanine transaminase; NTDT, non-transfusion-dependent thalassemia; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal.				

Proteinuria

In clinical studies, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio greater than 0.6 mg/mg) occurred in 18.6% of deferasirox-treated patients compared to 7.2% of deferoxamine- treated patients in Study 1 *[see Warnings and Precautions]*.

Other Adverse Reactions

In the population of more than 5,000 patients with transfusional iron overload who have been treated with deferasirox 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, laryngeal pain, cataract, hearing loss, GI hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, renal tubular disorder (Fanconi's syndrome), and acute pancreatitis (with and without underlying biliary conditions). 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, GI disorders, infections, increased serum creatinine, and increased serum transaminases.

Post-Marketing Experience

The following adverse reactions have been spontaneously reported during post-approval use of deferasirox 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, toxic epidermal necrolysis (TEN)

Immune system disorders: hypersensitivity reactions (including anaphylactic reaction and angioedema)

Renal and urinary disorders: acute renal failure, tubulointerstitial nephritis

Hepatobiliary disorders: hepatic failure

GI disorders: GI perforation

Blood and lymphatic system disorders: worsening anemia

DRUG INTERACTIONS

Aluminum-Containing Antacid Preparations

The concomitant administration of DEFERASIROX (JADENU®) and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, do not take DEFERASIROX (JADENU®) with aluminum-containing antacid preparations.

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]*.

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 DEFERASIROX (JADENU®) 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 DEFERASIROX (JADENU®) is coadministered with other CYP2C8 substrates *[see Clinical Pharmacology]*.

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 DEFERASIROX (JADENU®). Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with DEFERASIROX (JADENU®). Closely monitor patients for signs of exposure related toxicity when DEFERASIROX (JADENU®) is coadministered with other drugs metabolized by CYP1A2 *[see Clinical Pharmacology]*.

Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism

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

Bile Acid Sequestrants

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

Busulfan

Increased exposure of busulfan was observed with concomitant use with deferasirox. Monitor plasma concentrations of busulfan when coadministered with deferasirox to allow dose adjustment of busulfan as needed [*see Clinical Pharmacology*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no studies with the use of DEFERASIROX (JADENU®) in pregnant women to inform drug-associated risks.

Administration of deferasirox to rats during pregnancy resulted in decreased offspring viability and an increase in renal anomalies in male offspring at doses that were about or less than the recommended human dose on a mg/m^2 basis. No fetal effects were noted in pregnant rabbits at doses equivalent to the human recommended dose on a mg/m^2 basis. DEFERASIROX (JADENU®) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In embryo-fetal developmental studies, pregnant rats and rabbits received oral deferasirox during the period of organogenesis at doses up to 100 mg/kg/day in rats and 50 mg/kg/day in rabbits (1.2 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 of 10, 30, and 90 mg/kg/day (0.1, 0.3, and 1.0 times the MRHD on a mg/m^2 basis). Maternal toxicity, loss of litters, and decreased offspring viability occurred at 90 mg/kg/day (1.0 times the MRHD on a mg/m^2 basis), and increases in renal anomalies in male offspring occurred at 30 mg/kg/day (0.3 times the MRHD on a mg/m^2 basis).

Lactation

Risk Summary

No data are available regarding the presence of DEFERASIROX (JADENU®) or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. 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 breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Females and Males of Reproductive Potential

Contraception

Counsel patients to use non-hormonal method(s) of contraception since DEFERASIROX (JADENU®) can render hormonal contraceptives ineffective [see *Drug Interactions*].

Pediatric Use

Of the 700 patients with transfusional iron overload who received deferasirox during clinical studies, 292 were pediatric patients 2 to less than 16 years of age with various congenital and acquired anemias, including 52 patients age 2 to less than 6 years, 121 patients age 6 to less than 12 years and 119 patients age 12 to less than 16 years. Seventy percent of these patients had beta-thalassemia. Children between the ages of 2 to less than 6 years have a systemic exposure to deferasirox approximately 50% of that of adults *[see Clinical Pharmacology]*. However, the safety and efficacy of deferasirox 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, Indications, Dosage and Administration]*.

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 less than 16 years of age) with chronic iron overload and NTDT were treated with deferasirox in clinical studies. The safety and efficacy of deferasirox 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, Indications, Dosage and Administration]*.

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.

Monitoring recommendations for all pediatric patients with Transfusional Iron Overload and NTDT

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation *[see Warnings and Precautions]*.

Geriatric Use

Four hundred thirty-one (431) patients greater than or equal to 65 years of age were studied in clinical trials of deferasirox in the transfusional iron overload setting. Two hundred twenty-five (225) of these patients were between 65 and 75 years of age while 206 were greater than or equal to 75 years of age. 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.

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 DEFERASIROX (JADENU®) therapy.

Renal Impairment

For patients with creatinine clearance (CLcr) 40 to 60 mL/min, reduce the starting dose by 50% *[see Dosage and Administration, Clinical Pharmacology]*. DEFERASIROX (JADENU®) is contraindicated in patients with a CLcr less than 40 mL/min or serum creatinine greater than two times the age-appropriate upper limit of normal (ULN) *[see Contraindications]*.

DEFERASIROX (JADENU®) can cause renal failure. Monitor serum creatinine and calculate creatinine clearance during treatment in all patients. Reduce, interrupt or discontinue DEFERASIROX (JADENU®) dosing based on increases in serum creatinine *[see Dosage and Administration, Warnings and Precautions]*.

Hepatic Impairment

Avoid use in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, reduce the starting dose 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, Warnings and Precautions, Clinical Pharmacology]*.

OVERDOSAGE

Cases of overdose (2 to 3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved without long-term consequences after a dose interruption. Single doses of 80 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 56 mg/kg DEFERASIROX (JADENU®)) in iron overloaded thalassemic patients have been tolerated, with only mild nausea and diarrhea noted. Single doses up to 40 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 28 mg/kg DEFERASIROX (JADENU®)) in normal subjects have been well tolerated.

Early signs of acute overdose are digestive effects such as abdominal pain, diarrhea, nausea, and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.

There is no specific antidote for DEFERASIROX (JADENU®). In case of overdose, it may be treated with induction of vomiting or gastric lavage, and by symptomatic treatment.

CLINICAL PHARMACOLOGY

Mechanism of action

DEFERASIROX (JADENU®) 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.

Pharmacodynamics (PD)

Pharmacodynamic effects tested in an iron balance metabolic study with the tablet for oral suspension formulation 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 to 0.5 mg per kg per day). Iron excretion was predominantly fecal.

Cardiac Electrophysiology

The effect of 20 and 40 mg per kg per day of deferasirox (tablets for oral suspension) 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 subjects age 18 to 65 years. No evidence of prolongation of the QTc interval was observed in this study.

Pharmacokinetics (PK)

Absorption

Based on studies in patients with the tablet for oral suspension, deferasirox is absorbed following oral administration with median times to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. In healthy subjects, DEFERASIROX (JADENU®) showed comparable t_{max}. The maximal concentrations (C_{max}) and area under the curve ($AUC_{0\text{-}24h}$, AUC_{τ}) 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 to 2.3 after multiple doses with the tablet for oral suspension formulation.

Tablets

The absolute bioavailability [as measured by area under the curve over time to infinity (AUC_{inf})] of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (as measured by AUC_{inf}) of DEFERASIROX (JADENU®) tablets was 36%

greater than with deferasirox tablets for oral suspension. After strength- adjustment, the mean AUC_{inf} of DEFERASIROX (JADENU®) tablets (i.e., 360 mg strength) was similar to that of deferasirox tablets for oral suspension (i.e., 500 mg strength) under fasting conditions; however the mean C_{max} was increased by 30%. The 30% increase in C_{max} observed with DEFERASIROX (JADENU®) tablets is not clinically meaningful.

The administration of DEFERASIROX (JADENU®) tablets with a light meal (approximately 250 calories with fat content less than 7% of total calories) indicated that the AUC_{inf} and C_{max} were similar to that under fasting conditions. The administration of DEFERASIROX (JADENU®) tablets with a high-fat meal (approximately 1000 calories with fat content greater than 50% of total calories), increased AUC_{inf} by 18% and C_{max} by 29% compared to that under fasting conditions *[see Dosage and Administration]*.

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 is14.37 ± 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 subjects 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_{inf}) 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 dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration.

Drug Interactions

Midazolam: The concomitant administration of deferasirox tablets for oral suspension and CYP3A4 probe substrate midazolam resulted in a decrease of midazolam C_{max} by 23% and AUC_{inf} by 17%. In the clinical setting, this effect may be more pronounced, as the study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox *[see Drug Interactions]*.

Repaglinide: The concomitant administration of deferasirox tablets for oral suspension (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) increased repaglinide AUC_{inf} to 2.3 fold and C_{max} of 1.6-fold *[see Drug Interactions]*.

Theophylline: The concomitant administration of deferasirox tablets for oral suspension (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_{inf} 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]*.

Rifampicin: The concomitant administration of deferasirox tablets for oral suspension (single dose of 30 mg per kg) and the strong uridine diphosphate glucuronosyltransferase (UGT) inducer rifampicin (600 mg per day for 9 days) decreased deferasirox AUC_{inf} by 44% *[see Drug Interactions]*.

Cholestyramine: The concomitant administration of cholestyramine after a single dose of deferasirox tablets for oral suspension decreased deferasirox AUC_{inf} by 45% *[see Drug Interactions]*.

Busulfan: Concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC).

In vitro studies: Deferasirox inhibited human CYP2A6, CYP2D6, and CYP2C19 in vitro. Deferasirox is not a substrate of P-glycoprotein, MRP1 or MRP2.

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 less than 6 years of age, systemic exposure was about 50% lower than in adults.

Sex: The apparent clearance is 17.5% lower in females compared to males.

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

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_{inf} 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.

NONCLINICAL TOXICOLOGY

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/kg/day (0.7 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/kg/day (1.2 times the MRHD on a mg/m^2 basis) in males and 300 mg/kg/day (1.7 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/kg/day (0.9 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.

CLINICAL STUDIES

DEFERASIROX (JADENU®) was evaluated in healthy subjects. There are no clinical data in patients with DEFERASIROX (JADENU®). DEFERASIROX (JADENU®) contains the same active ingredient as Exjade (deferasirox) tablets for oral suspension. The following information is based on clinical trials conducted with Exjade tablets for oral suspension.

Transfusional Iron Overload

The primary efficacy study, Study 1 (NCT00061750), was a multicenter, open-label, randomized, active-comparator control study to compare deferasirox tablets for oral suspension and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients greater than or equal to 2 years of age were randomized in a 1:1 ratio to receive either oral deferasirox tablets for oral suspension at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous deferoxamine at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2 to 3, greater than 3 to 7, greater than 7 to 14, and greater than 14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values less than 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 greater than or equal to 3 mg Fe/g dry weight for baseline values greater than or equal to 10 mg Fe/g dry weight, reduction of baseline values between 7 and less than 10 to less than 7 mg Fe/g dry weight, or maintenance or reduction for baseline values less than 7 mg Fe/g dry weight.

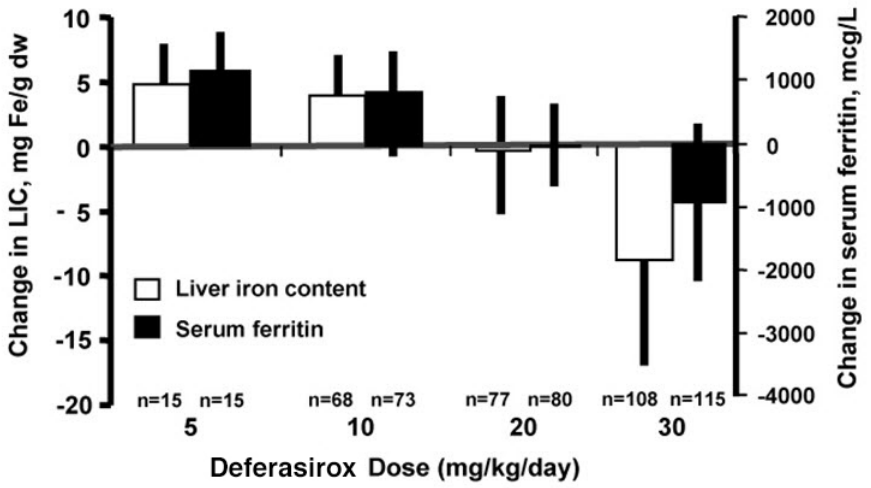
A total of 586 patients were randomized and treated, 296 with deferasirox tablets for oral suspension and 290 with deferoxamine. The mean age was 17.1 years (range, 2 to 53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (deferasirox tablets for oral suspension n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse reaction. The percentage of patients achieving the primary endpoint was 52.9% for deferasirox tablets for oral suspension and 66.4% for deferoxamine. The relative efficacy of deferasirox 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 deferasirox tablets for oral suspension and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with deferasirox tablet for oral suspension doses of 20 to 30 mg per kg per day. Deferasirox tablets for oral suspension 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]*.

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox Tablets for Oral Suspension (5 to 30 mg per kg per day) in Study 1



Study 2 (NCT00061763) was an open-label, noncomparative trial of efficacy and safety of deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension 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). Nineteen percent (19%) of patients were less than 16 years of age and 16% were greater than or equal to 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 (NCT00067080) was a multicenter, open-label, randomized trial of the safety and efficacy of deferasirox tablets for oral suspension relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension and 63 with deferoxamine. Forty-four percent of patients were less than 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 deferasirox tablets for oral suspension (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 magnetic resonance imaging (MRI) T2* value

(measured in milliseconds, [ms]) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to less than 20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of deferasirox tablets for oral suspension 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 (less than 10 ms) and in those with mild to moderate cardiac iron overload (greater than or equal to 10 to less than 20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven (627) 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 deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension.

Study 4 (TELESTO; NCT 00940602) was a double-blind, placebo-controlled, randomized trial performed in 225 patients with MDS (Low/Int-1 risk) and transfusional iron overload of which 149 were treated with deferasirox and 76 received placebo. The observed hazard ratio of 0.64 (95% CI: 0.42, 0.96) suggests a positive impact of deferasirox on event-free survival (EFS, a composite endpoint defined as death, worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, or progression to acute myeloid leukemia, whichever occurred first).

Non-Transfusion-Dependent Thalassemia

Study 5 (NCT00873041) was a randomized, double-blind, placebo-controlled trial of treatment with deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension 5 mg/kg/day dose group, 55 to the deferasirox tablets for oral suspension 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 to 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 deferasirox dose groups compared with placebo (p less than or equal to 0.001) (Table 5). Furthermore, a statistically significant dose effect of deferasirox 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.

Study 6 (NCT00873041) was an open-label trial of deferasirox tablets for oral suspension for the treatment of patients previously enrolled on Study 5, including cross-over to active treatment for those previously treated with placebo. The starting dose of deferasirox tablets for oral suspension in Study 6 was assigned based on the patient's LIC at completion of Study 5, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3 to 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 6 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 6 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 6, 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 below.

Study 7 (NCT01709838) was an open-label, single-arm, multi-center, 5-year study to evaluate the efficacy and safety of deferasirox tablets for oral suspension in iron overloaded patients with NTDT of 10 years of age or older. All patients started treatment on 10 mg/kg/day deferasirox tablets for oral suspension for four weeks. At Week 4, dose escalation was based on baseline LIC. At Week 24 and every 6 months thereafter, further dose adjustments were made according to the LIC at that visit. Treatment was interrupted when LIC < 3 mg Fe/g dw or serum ferritin < 300 ng/mL and was re-started at 10 mg/kg/day when LIC ≥ 5 mg Fe/g dw and serum ferritin ≥ 300 ng/mL. Throughout the study, the maximum dose of deferasirox tablets for oral suspension given was 30 mg/kg/day.

A total of 134 patients were enrolled in the study. Eligible patients were required to have an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin at least of 300 ng/mL at screening. The mean absolute change of LIC from Baseline to Week 52 was -6.7 mg Fe/g dw. The reduction in LIC was sustained until Week 260 (5 years) with the mean absolute change in LIC from Baseline to Week 260 of -10.6 mg Fe/g dw. In the subset of patients with Baseline LIC > 15 mg Fe/g dw (49 patients), 51.0% achieved a first LIC < 5 mg Fe/g dw (95% CI: 37.5, 64.4) with a median time of 28.6 months. In the subset of patients with target LIC of < 3 mg Fe/g dw (61 patients), 39.3% developed first LIC ≥ 5 mg Fe/g dw in the follow-up period, with a median time of 13.9 months.

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

	Deferasirox tablets for oral suspension Starting Dose[a]

	Placebo	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Study 5[b]				
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	+0.4	-2.0	-3.8	-
(95% Confidence Interval)	(-0.6,+1.3)	(-2.9, -1.0)	(-4.8, -2.9)	-
Study 6				
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	-	-1.5	-2.8	-9.1
(95% Confidence Interval)	-	(-3.7, +0.7)	(-3.4, -2.2)	(-11.0, -7.3)
Study 7				
Number of Patients	-	-	n = 127	-
Mean LIC at Baseline (mg Fe/ g dw)	-	-	15.1	-
Mean Change (mg Fe/ g dw)	-	-	-6.7	-
(95% Confidence Interval)	-	-	(-7.9, -5.5)	-

Abbreviation: LIC, liver iron concentration; NTDT, non-transfusion-dependent thalassemia.

[a]Randomized dose in Study 5 or assigned starting dose in Study 6 and Study 7

[b]Least square mean change for Study 5

INCOMPATIBILITIES

Not applicable.

PATIENT COUNSELING INFORMATION

Blood Testing

Advise patients that blood tests will be performed frequently to check for damage to kidneys, liver, or blood cells *[see Warnings and Precautions].* **Acute Kidney Injury, Including Acute Renal Failure**

Caution patients about the potential for kidney toxicity when taking DEFERASIROX (JADENU®). Inform patients of the signs and symptoms of kidney injury. Advise patients to contact their healthcareprovider immediately if they experience any of these symptoms *[see Warnings and Precautions].*

Hepatic Toxicity and Failure

Caution patients about the potential for hepatic toxicity when taking DEFERASIROX (JADENU®). Inform patients of the signs and symptoms of hepatic toxicity. Advise patients to contact their healthcare provider immediately if they experience any of these symptoms *[see Warnings and Precautions]*.

GI Ulceration and Hemorrhage

Caution patients about the potential for the development of GI ulcers or bleeding when taking DEFERASIROX (JADENU®) in combination with drugs that have ulcerogenic or hemorrhagic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants. Inform patients of the signs and symptoms of GI ulcers or bleeding. Advise patients to contact their healthcare provider for symptoms of heartburn but to seek immediate medical attention for symptoms of GI hemorrhage *[see Warnings and Precautions]*.

Skin and Allergic Reactions

Skin rashes may occur during DEFERASIROX (JADENU®) treatment and if severe, interrupt treatment. Serious allergic reactions (which include swelling of the throat) have been reported in patients taking DEFERASIROX (JADENU®), usually within the first month of treatment. If reactions are severe, advise patients to stop taking DEFERASIROX (JADENU®) and contact their doctor immediately *[see Warnings and Precautions]*.

Pediatric Patients with Acute Illness

Instruct pediatric patients and their caregivers to contact their healthcare provider during episodes of acute illness, especially if the patient has not been drinking fluids or the patient has volume depletion due to fever, vomiting, or diarrhea *[see Warnings and Precautions]*.

Auditory and Ocular Testing

Because auditory and ocular disturbances have been reported with deferasirox, conduct auditory testing and ophthalmic testing before starting DEFERASIROX (JADENU®) treatment and thereafter at regular intervals. Advise patients to contact their healthcare provider if they develop visual or auditory changes during treatment *[see Warnings and Precautions]*.

Drug Interactions

Caution patients not to take aluminum containing antacids and DEFERASIROX (JADENU®) tablets simultaneously [*see Drug Interactions*].

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

Caution patients about potential loss of effectiveness of DEFERASIROX (JADENU®) 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 DEFERASIROX (JADENU®) when concomitantly used with potent UGT inducers [see *Drug Interactions*].

Caution patients about potential loss of effectiveness of DEFERASIROX (JADENU®) 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 DEFERASIROX (JADENU®) when concomitantly used with bile acid sequestrants *[see Drug Interactions]*.

Dosing Instructions

Advise patients to take DEFERASIROX (JADENU®) tablets with water or other liquids. Advise patients to swallow DEFERASIROX (JADENU®) tablets once daily with water or other liquids, preferably at the same time each day. Advise patients to take DEFERASIROX (JADENU®) tablets on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/lettuce, tomato, and 1 packet mustard). For patients who have difficulty swallowing whole tablets, DEFERASIROX (JADENU®) tablets may be crushed and mixed with soft foods (e.g., yogurt or apple sauce) immediately prior to use and administered orally. Advise against the use of commercial crushers with serrated surfaces for crushing a single 90 mg tablet. Advise patients to immediately and completely consume the dose and not store it for future use *[see Dosage and Administration]*.

Handling Instructions

Advise patients to store DEFERASIROX (JADENU®) in a dry, room-temperature environment.

Driving and Using Machines

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

STORAGE

Store at temperatures not exceeding 30°C.

DEFERASIROX (JADENU®) should not be used after the date marked "EXP" on the pack.

INSTRUCTIONS FOR USE AND HANDLING

DEFERASIROX (JADENU®) must be kept out of the reach and sight of children.

AVAILABILITY

PVC/PVDC blister pack (2-layer PVC/PVDC-film Duplex) backed with heat sealable lacquered aluminum foil x 10's (Box of 30's)

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Registration Number/Date of Registration:
90 mg Film-coated tablet: DR-XY46255 / 19 June 2018
180 mg Film-coated tablet: DR-XY46254 / 19 June 2018

360 mg Film-coated tablet: DR-XY46253 / 19 June 2018

Manufactured by:
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