

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207968Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JADENU safely and effectively. See full prescribing information for JADENU.

JADENU® (deferasirox) tablets, for oral use

JADENU® Sprinkle (deferasirox) granules, for oral use

Initial U.S. Approval: 2005

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

See full prescribing information for complete boxed warning.

JADENU may cause serious and fatal:

- renal toxicity, including failure (5.1)
- hepatic toxicity, including failure (5.2)
- gastrointestinal hemorrhage (5.3)

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

RECENT MAJOR CHANGES

Dosage and Administration, Administration (2.3)	5/2017
Warnings and Precautions, Hypersensitivity (5.6)	8/2016
Warnings and Precautions, Severe Skin Reactions (5.7)	8/2016

INDICATIONS AND USAGE

JADENU 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 approved under accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

JADENU 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 (Fe/g dw) and a serum ferritin greater than 300 mcg/L. This indication is approved under accelerated approval based on a reduction of liver iron concentrations (to less than 5 mg Fe/g dw) and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.2)

Limitations of Use

Controlled clinical trials of JADENU 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 JADENU when administered with other iron chelation therapy have not been established. (1.3)

DOSAGE AND ADMINISTRATION

- Transfusional iron overload: Initial dose 14 mg/kg (calculated to nearest whole tablet or nearest whole sachet content for granules) once daily. (2.1)
- NTDT syndromes: Initial dose 7 mg/kg (calculated to nearest whole tablet or nearest whole sachet content for granules) once daily. (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)
- Take on an empty stomach or with a light meal. Sprinkle JADENU Sprinkle granules on soft foods (2.3)

- Reduce dose for moderate (Child-Pugh B) hepatic impairment by 50%. Avoid in patients with severe (Child-Pugh C) hepatic impairment. (2.4)
- Reduce dose by 50% in patients with renal impairment (CLcr 40–60 mL/min). (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg, 180 mg, 360 mg. (3)

Granules: 90 mg, 180 mg, 360 mg. (3)

CONTRAINDICATIONS

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal (ULN) or creatinine clearance (CLcr) 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 less than $50 \times 10^9/L$. (4)
- Known hypersensitivity to deferasirox or any component of JADENU. (4)

WARNINGS AND PRECAUTIONS

- Bone marrow suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during JADENU therapy. Interrupt therapy for toxicity. (5.4)
- Increased Toxicity in the Elderly: Monitor closely for toxicity. (5.5)
- Hypersensitivity Reactions: Discontinue JADENU for severe reactions and institute medical intervention. (5.6)
- Severe skin reactions including Stevens-Johnson syndrome: Discontinue JADENU. (5.7)

ADVERSE REACTIONS

In patients with transfusional iron overload, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In deferasirox-treated patients with NTDT syndromes, the most frequently occurring (greater than 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 JADENU with aluminum-containing antacid preparations. (7.1)
- Deferasirox increases the exposure of repaglinide. Consider repaglinide dose reduction and monitor blood glucose levels. (7.3)
- Avoid the use of JADENU with theophylline as theophylline levels could be increased. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Lactation: Discontinue drug or breastfeeding, taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2017

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FULL PRESCRIBING INFORMATION

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **JADENU 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 (CL_{cr}) 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

- **JADENU 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 JADENU 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

- **JADENU 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 JADENU 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)

JADENU 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 approved under accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels [see *Clinical Studies* (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

JADENU 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 approved under accelerated approval based on a reduction of liver iron concentrations (to less than 5 mg Fe/g dw) and serum ferritin levels [see *Clinical Studies* (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.3 Limitations of Use

Controlled clinical trials of JADENU 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 JADENU when administered with other iron chelation therapy have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Transfusional Iron Overload

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 1000 mcg/L.

Prior to starting therapy, obtain:

- serum ferritin level
- baseline serum creatinine in duplicate (due to variations in measurements) and determine the CL_{Cr} (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 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 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 2500 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 JADENU [see *Warnings and Precautions* (5.10)].

2.2 Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

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* (14)]
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the CL_{Cr} (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 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. 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 (5.1, 5.2, 5.4)*].

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

2.3 Administration

Swallow JADENU tablets once daily with water or other liquids, preferably at the same time each day. Take 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 JADENU tablets with aluminum-containing antacid products [*see Drug Interactions (7.1)*]. For patients who have difficulty swallowing whole tablets, 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.

Take JADENU Sprinkle granules on an empty stomach or with a light meal [*see Pharmacokinetics (12.3)*]. Administer JADENU Sprinkle granules by sprinkling the full dose on soft food (e.g. yogurt or apple sauce) immediately prior to use and administered orally. JADENU Sprinkle granules should be taken once a day, preferably at the same time each day. Do not take JADENU Sprinkle granules with aluminum-containing antacid products [*see Drug Interactions (7.1)*].

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

	EXJADE Tablets for oral suspension (white round tablet)	JADENU Tablets (film coated blue oval tablet) JADENU Sprinkle Granules (white to almost white granules)
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

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 JADENU tablets or JADENU Sprinkle granules [see *Warnings and Precautions (5.2)*, *Use in Specific Populations (8.7)*].

Patients with Baseline Renal Impairment

For patients with CL_{Cr} 40 to 60 mL/min, reduce the starting dose by 50% [see *Use in Specific Populations (8.6)*]. Do not use JADENU in patients with serum creatinine greater than two times the age-appropriate upper limit of normal (ULN) or CL_{Cr} less than 40 mL/min [see *Contraindications (4)*].

2.5 Dose Modifications for Increases in Serum Creatinine

For serum creatinine increases while receiving JADENU [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 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 (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 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 (4)*].

2.6 Dose Modifications Based on Concomitant Medications

UDP-glucuronosyltransferases (UGT) Inducers

Concomitant use of UGT inducers decreases systemic exposure. Avoid the concomitant use of strong UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). If you must administer JADENU tablets or JADENU Sprinkle granules with a strong UGT inducer, consider increasing the initial dose 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 systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colestevam, colestipol). If you must administer JADENU tablets or JADENU Sprinkle granules with a bile acid sequestrant, consider increasing the initial dose 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

- 90 mg JADENU tablets
Light blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '90' on a slight upward slope in between two debossed curved lines on the other side.
- 180 mg JADENU tablets
Medium blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '180' on a slight upward slope in between two debossed curved lines on the other side.
- 360 mg JADENU tablets
Dark blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '360' on a slight upward slope in between two debossed curved lines on the other side.
- 90 mg JADENU Sprinkle granules
Supplied in cartons containing 30 child resistant foil sachets. Each sachet contains 162 mg of white to almost white granules, equivalent to 90 mg deferasirox.
- 180 mg JADENU Sprinkle granules

Supplied in cartons containing 30 child resistant foil sachets. Each sachet contains 324 mg of white to almost white granules, equivalent to 180 mg deferasirox.

- 360 mg JADENU Sprinkle granules

Supplied in cartons containing 30 child resistant foil sachets. Each sachet contains 648 mg of white to almost white granules, equivalent to 360 mg deferasirox.

4 CONTRAINDICATIONS

JADENU is contraindicated in patients with:

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

5 WARNINGS AND PRECAUTIONS

5.1 Renal Toxicity, Renal Failure, and Proteinuria

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 (6.1, 6.2)*].

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 (2.5)*].

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.

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 (6.1)*].

5.2 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* (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 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* (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 deferasirox [see *Adverse Reactions* (6.1)]. Monitor for signs and symptoms of GI ulceration and hemorrhage during JADENU 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 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 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 deferasirox. Preexisting hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with JADENU in patients who develop cytopenias until the cause of the cytopenia has been determined. JADENU is contraindicated in patients with platelet counts below $50 \times 10^9/L$.

5.5 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 JADENU more frequently for toxicity [see *Use in Specific Populations* (8.5)].

5.6 Hypersensitivity

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* (6.2)]. If reactions are severe, discontinue JADENU and institute appropriate medical intervention. 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.

5.7 Severe Skin Reactions

Severe skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme, have been reported during deferasirox therapy [see *Adverse Reactions* (6.2)]. The risk of other skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be

excluded. If severe skin reactions are suspected, discontinue JADENU immediately and do not reintroduce JADENU therapy.

5.8 Skin Rash

Rashes may occur during JADENU treatment [see *Adverse Reactions (6.1)*]. For rashes of mild to moderate severity, JADENU may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with JADENU. 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 less than 1% with deferasirox therapy in the clinical studies. Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting JADENU 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 JADENU, since overchelation may increase JADENU 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 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 JADENU and obtain a confirmatory LIC [see *Clinical Studies (14)*].

6 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 (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)*]

6.1 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. JADENU was evaluated in healthy volunteer trials. Currently, there are no clinical data in patients with JADENU tablets and JADENU Sprinkle granules. 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 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 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* Occurring in >5% of Deferasirox-treated Patients in Study 1, Study 3, and MDS Pool

Preferred Term	Study 1 (Beta-thalassemia)		Study 3 (Sickle Cell Disease)		MDS Pool
	Deferasirox N=296 n (%)	Deferoxamine N=290 n (%)	Deferasirox N=132 n (%)	Deferoxamine N=63 n (%)	Deferasirox 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 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 (5.1)*]. In this study, 17 (6%) patients treated with deferasirox developed elevations in SGPT/ALT levels greater than 5 times the 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 (5.2)*]. 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 (5.1)*]. 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 (5.1)*]. 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 (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	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 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 deferasirox 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 deferasirox 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 greater than 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
	Deferasirox	Placebo	Deferasirox
	N=110	N=56	N=130
	n (%)	n (%)	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 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 4.

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

	Study 4		Study 5
	Deferasirox	Placebo	Deferasirox
	N=110	N=56	N=130
Laboratory Parameter	n (%)	n (%)	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 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 (5.1)*].

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, gastrointestinal 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, 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 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

Gastrointestinal disorders: gastrointestinal perforation

Blood and lymphatic system disorders: worsening anemia

7 DRUG INTERACTIONS

7.1 Aluminum Containing Antacid Preparations

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

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 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 JADENU 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 JADENU. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with JADENU. Closely monitor patients for signs of exposure related toxicity when JADENU 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 JADENU with strong UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in JADENU efficacy due to a possible decrease in deferasirox concentration. Avoid the concomitant use of strong UGT inducers with JADENU. Consider increasing the initial dose of JADENU 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, colestevlam, colestipol) with JADENU due to a possible decrease in deferasirox concentration. If you must coadminister these agents together, consider increasing the initial dose of JADENU [see *Dosage and Administration* (2.5), *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with the use of 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/m² basis. No fetal effects were noted in pregnant rabbits at doses equivalent to the human recommended dose on a mg/m² basis. 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/m² 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/m² basis). Maternal toxicity, loss of litters, and decreased offspring viability occurred at 90 mg/kg/day (1.0 times the MRHD on a mg/m² basis), and increases in renal anomalies in male offspring occurred at 30 mg/kg/day (0.3 times the MRHD on a mg/m² basis).

8.2 Lactation

Risk Summary

No data are available regarding the presence of 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.

8.4 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 (12.3)*]. 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 (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 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 (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 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 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.

8.6 Renal Impairment

For patients with creatinine clearance (CL_{cr}) 40 to 60 mL/min, reduce the starting dose by 50% [see *Dosage and Administration* (2.4), *Clinical Pharmacology* (12.3)]. JADENU is contraindicated in patients with a CL_{cr} less than 40 mL/min or serum creatinine greater than two times the age-appropriate upper limit of normal (ULN) [see *Contraindications* (4)].

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

8.7 Hepatic Impairment

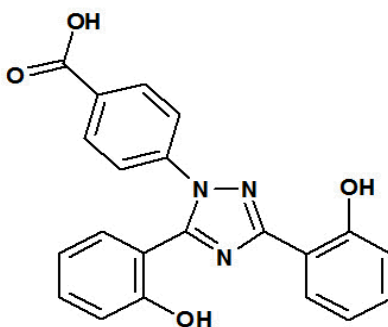
Avoid use in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, reduce the starting dose by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.2), *Pharmacokinetics* (12.3)].

10 OVERDOSAGE

Cases of overdose (2 to 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 of deferasirox up to 80 mg per kg per day with the tablet for oral suspension formulation in iron overloaded beta-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy subjects, single doses of up to 40 mg per kg per day with the tablet for oral suspension formulation were tolerated. There is no specific antidote for JADENU. In case of overdose, induce vomiting and employ gastric lavage.

11 DESCRIPTION

JADENU (deferasirox) is an iron chelating agent provided as a tablet for oral use. Deferasirox is designated chemically as 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid and has the following structural formula:



Deferasirox is a white to slightly yellow powder. It has a molecular formula C₂₁H₁₅N₃O₄ and molecular weight of 373.4. It is insoluble in water with a pH of suspension of 4.1.

JADENU tablets contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include microcrystalline cellulose, crospovidone, povidone (K30), magnesium stearate, colloidal silicon dioxide, and poloxamer (188). The film coating contains opadry blue.

JADENU Sprinkle granules contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include microcrystalline cellulose, crospovidone; povidone (K30), magnesium stearate, colloidal silicon dioxide, poloxamer (188).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JADENU (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 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.

12.3 Pharmacokinetics

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, JADENU showed comparable t_{max} . The maximal concentrations (C_{max}) and area under the curve ($\text{AUC}_{0-24\text{h}}$, 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 JADENU tablets was 36% greater than with deferasirox tablets for oral suspension. After strength-adjustment, the mean AUC_{inf} of 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 JADENU tablets is not clinically meaningful.

The administration of 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 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* (2.3)].

Granules

The bioavailability (as measured by AUC_{inf}) of JADENU Sprinkle granules was 52% greater than with deferasirox tablets for oral suspension. After strength-adjustment, the mean AUC_{inf} of the JADENU Sprinkle granules (i.e., 4 x 90_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 34%. The 34% increase in C_{max} observed with JADENU Sprinkle granules is not clinically meaningful.

The administration of JADENU Sprinkle granules with a soft meal (e.g., yogurt and apple sauce) or with a low-fat (approximately 450 calories with fat content approximately 30% of total calories) indicated that the AUC_{inf} and C_{max} after a low-fat meal or soft foods were similar to that under fasting conditions. The administration of JADENU Sprinkle granules with a high-fat meal (approximately 1000 calories with fat content greater than 50% of total calories) increased AUC_{inf} by 18% with no changes in C_{max} compared to that under fasting conditions [see *Dosage and Administration* (2.3)].

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 glucuronides 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* (7.2)].

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* (7.3)].

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* (7.4)].

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* (7.5)].

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 (7.6)*].

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.

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/kg/day (0.7 times the MRHD on a mg/m² 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/m² basis) in males and 300 mg/kg/day (1.7 times the MRHD on a mg/m² 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/m² basis) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

JADENU was evaluated in healthy subjects. There are no clinical data in patients with JADENU. 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, 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 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 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.

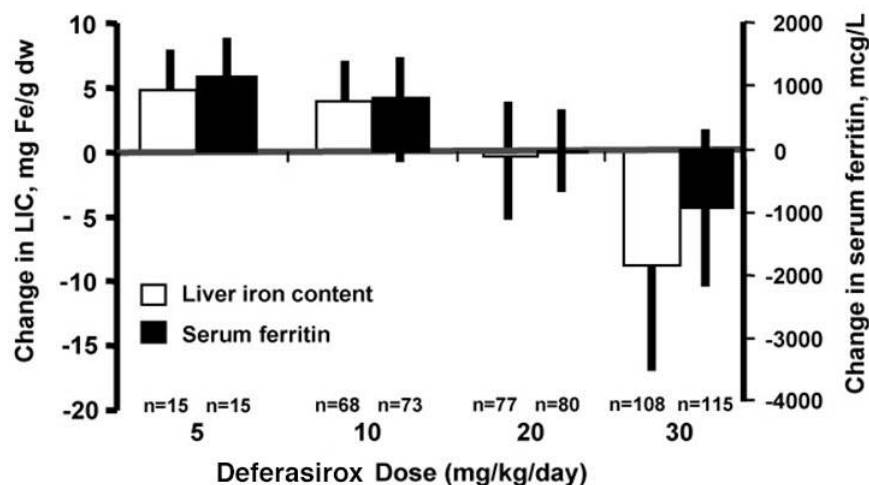
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of greater than or equal to 3 mg Fe/g dry weight for baseline values greater than or equal to 10 mg Fe/g dry weight, reduction of baseline values 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 event. 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 (2.1)*].

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 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). 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 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 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 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 ($\pm$ 2615.59) mcg/L (n=593) and mean change in LIC was -5.9 ($\pm$ 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. No controlled trials have been performed to demonstrate that these reductions improve morbidity or mortality in patients with MDS. Adverse reactions with deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension therapy.

Non-Transfusion-Dependent Thalassemia

Study 4 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.

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

	Deferasirox tablets for oral suspension Starting Dose¹			
	Placebo	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Study 4²				
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 deferasirox tablets for oral suspension 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 deferasirox tablets for oral suspension 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 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 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

JADENU 90 mg tablets are light blue in color, film-coated, oval biconvex tablets with beveled edges, debossed with 'NVR' on one side and '90' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0654-15).

JADENU 180 mg tablets are medium blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with 'NVR' on one side and '180' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0655-15).

JADENU 360 mg tablets are dark blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with 'NVR' on one side and '360' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0656-15).

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

JADENU Sprinkle 90 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0727-15).

JADENU Sprinkle 180 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0713-15).

JADENU Sprinkle 360 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0720-15).

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

17 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* (5.1, 5.2, 5.3, 5.4, 5.5)].

Gastrointestinal Ulceration and Hemorrhage

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

Skin and Allergic Reactions

Skin rashes may occur during JADENU treatment and if severe, interrupt treatment. Serious allergic reactions (which include swelling of the throat) have been reported in patients taking JADENU, usually within the first month of treatment. If reactions are severe, advise patients to stop taking JADENU and contact their doctor immediately [see *Warnings and Precautions* (5.6, 5.7, 5.8)].

Auditory and Ocular Testing

Because auditory and ocular disturbances have been reported with deferasirox, conduct auditory testing and ophthalmic testing before starting JADENU treatment and thereafter at regular intervals [see *Warnings and Precautions* (5.9)].

Drug Interactions

Caution patients not to take aluminum containing antacids and JADENU tablets or granules simultaneously [see *Drug Interactions* (7.1)].

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

Caution patients about potential loss of effectiveness of 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 JADENU when concomitantly used with potent UGT inducers [see *Drug Interactions* (7.5)].

Caution patients about potential loss of effectiveness of 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 JADENU when concomitantly used with bile acid sequestrants [see *Drug Interactions* (7.6)].

Dosing Instructions

Advise patients to take JADENU tablets with water or other liquids. Advise patients to swallow JADENU tablets once daily with water or other liquids, preferably at the same time each day. Advise patients to take 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, 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 (2.3)]*.

Advise patients to take JADENU Sprinkle granules by sprinkling the full dose on soft food (e.g., yogurt or apple sauce) immediately prior to use and administered orally. Advise patients to take JADENU Sprinkle granules once a day, preferably at the same time each day. JADENU Sprinkle granules may be taken on an empty stomach or with a light meal.

Handling Instructions

Advise patients to store JADENU in a dry, room-temperature environment *[see How Supplied/Storage and Handling (16)]*.

Driving and Using Machines

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

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/s/

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