PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTEVA-DEFERASIROX (TYPE J)

Deferasirox Tablets

Tablets, 90 mg, 180 mg, 360 mg; oral

Iron chelating agent

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RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-DEFERASIROX (TYPE J) (deferasirox) film-coated tablets is indicated for:

- the management of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older.

- the management of chronic iron overload in patients with transfusion-dependent anemias aged two to five who cannot be adequately treated with deferoxamine.

- the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

Therapy with TEVA-DEFERASIROX (TYPE J) should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

1.1 Pediatrics

Pediatrics (2 to 16 years of age): There are limited data available on the use of deferasirox in children aged 2 to 5 (see 7.1.3 Pediatrics). The overall exposure of deferasirox in young children (aged 2 to 5) was about 50% lower than in adults and this age group may require higher maintenance doses than are necessary in adults (see 4 DOSAGE AND ADMINISTRATION).

1.2 Geriatrics

Geriatrics (≥ 65 years of age)**:** Four hundred and thirty-one (431) patients ≥ 65 years of age have been studied in clinical trials of deferasirox (see 7.1.4 Geriatrics). The pharmacokinetics of deferasirox have not been studied in elderly patients. In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

2 CONTRAINDICATIONS

TEVA-DEFERASIROX (TYPE J) is contraindicated in:

- patients with estimated creatinine clearance <60 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal (ULN).

- high risk myelodysplastic syndrome (MDS) patients, any other MDS patient with a life expectancy < 1 year 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.

- patients with platelet counts < 50 x 10^9/L.

- patients with hypersensitivity to the active substance, deferasirox, or to any of the excipients. For a complete listing of excipients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Therapy with TEVA-DEFERASIROX (TYPE J) should be initiated and maintained by physicians experience in the treatment of chronic iron overload due to blood transfusions.

Deferasirox is contraindicated in patients with moderate and severe renal impairment (see 2 CONTRAINDICATIONS) and has not been studied in patients with severe hepatic impairment.

The following are clinically significant adverse events;

- Acute renal failure (see 7 WARNINGS AND PRECAUTIONS; Renal)
- Hepatic failure (see 7 WARNINGS AND PRECAUTIONS; Hepatic/Biliary/Pancreatic)
- Gastrointestinal haemorrhage and perforations (see 7 WARNINGS AND PRECAUTIONS; Gastrointestinal)

Deferasirox film-coated tablets is a strength-adjusted formulation of deferasirox with higher bioavailability compared to deferasirox dispersible tablets (see 10.3 Pharmacokinetics). TEVA-DEFERASIROX (TYPE J) requires a different dosing regimen and method of administration compared to deferasirox dispersible tablets. To avoid dosing errors, it is important that prescriptions of deferasirox specify both the type of formulation (dispersible tablet or film-coated tablet) and the prescribed dose in mg/kg/day.

This medicine is also available as a tablet that is meant to be dissolved in liquid before drinking. The doses of these two formulations are not the same. Be sure you are taking the right type of deferasirox. Check with your doctor, nurse or pharmacist if you are not sure.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Deferasirox film-coated tablets and deferasirox dispersible tablets for oral suspension are different formulations of deferasirox. Deferasirox film-coated tablets require a different dosing regimen and method of administration compared to deferasirox dispersible tablets for oral suspension. If converting from deferasirox dispersible tablets for oral suspension to deferasirox film-coated tablets, see the Dosing Considerations section below.
- **To avoid dosing errors, it is important that prescriptions of deferasirox specify both the type of formulation (dispersible tablets for oral suspension or film-coated tablets) and the prescribed dose in mg/kg/day.**

4.2 Recommended Dose and Dosage Adjustment

A. Transfusional iron overload

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

It is recommended that therapy with TEVA-DEFERASIROX (TYPE J) (deferasirox) be started when a patient has evidence of chronic iron overload, such as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40 kg patient) and a serum ferritin consistently >1000 mcg/L. Doses should be in mg/kg and must be calculated and rounded to the nearest whole tablet size. Changes in weight of pediatric patients over time must be taken into account when calculating the dose. TEVA-DEFERASIROX (TYPE J) is available in three strengths (90 mg, 180 mg and 360 mg).

a. Starting Dose

The recommended initial daily dose of TEVA-DEFERASIROX (TYPE J) is 7, 14 or 21 mg/kg/day body weight, depending on the patient's transfusion rate and the goal of treatment:

Patients requiring maintenance of an acceptable body iron level:

- An initial daily dose of 7 mg/kg/day is recommended for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult) and for whom the objective is maintenance of an acceptable body iron level.
- An initial daily dose of 14 mg/kg/day is recommended for patients receiving more than 7 mL/kg/month of packed red blood cells (approximately >2 units/month for an adult) and for whom the objective is maintenance of an acceptable body iron level.

Patients requiring reduction of iron overload:

- An initial daily dose of 14 mg/kg/day is recommended for patients receiving less than 14 mL/kg/month of packed red blood cells (approximately <4 units/month for an adult) and for whom the objective is gradual reduction of iron overload.
- An initial daily dose of 21 mg/kg/day is recommended for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately >4 units/month for an adult) and for whom the objective is gradual reduction of iron overload.

With deferasirox dispersible tablets for oral suspension, the dose dependent iron excretion (mg/kg/day) was calculated from the change in LIC over one year, the amount of blood transfused and the weight of the patient. Using two example patients of 20 kg and 50 kg, the amount of iron excreted over one year could be calculated in terms of mg/year and transfusion unit-equivalents/year (assuming that one unit of PRBC contains 200 mg iron). Thus in a 50 kg adult, deferasirox tablets for oral suspension doses of 10, 20 and 30 mg/kg (equivalent to deferasirox film-coated tablets 7, 14 and 21 mg, respectively) for one year can remove the amount of iron contained in about 20, 36 and 55 units of blood, respectively (i.e. about 1.5, 3 and 4.5 units of blood per month, respectively). In a 20

kg pediatric patient, deferasirox tablets for oral suspension doses of 10, 20 and 30 mg (equivalent to deferasirox film-coated tablets 7, 14 and 21 mg, respectively) for one year can remove the amount of iron contained in about 8, 14 and 22 units of blood, respectively (i.e. about 0.6, 1.2 and 1.8 units of blood per month; or 6, 12 and 18 mL/kg/month, respectively).

Table 1: Study 0107: Iron excretion during one year (PP-2 population, biopsy)*

Initial dose (mg/kg) Deferasirox tablets for oral suspension	Equivalent dose of Deferasirox film-coated tablets (mg/kg)	n	Iron excretion (mg/kg/day)	Iron excretion (mg/year)		Iron excretion (transfusion unit equivalents/year)	
				20 kg patient	50 kg patient	20 kg patient	50 kg patient
5	3.5	8	0.13 ± 0.10	939 ± 726	2349 ± 1816	4.7 ± 3.6	11.7 ± 9.1
10	7	44	0.22 ± 0.14	1572 ± 1055	3930 ± 2638	7.9 ± 5.3	19.6 ± 13.2
20	14	64	0.39 ± 0.15	2841 ± 1102	7102 ± 2756	14.2 ± 5.5	35.5 ± 13.8
30	21	108	0.60 ± 0.23	4378 ± 1712	10945 ± 4280	21.9 ± 8.6	54.7 ± 21.4

*the study was conducted with the tablet for oral suspension formulation (doses as in first column); the equivalent doses (in second column) for deferasirox film-coated tablets are provided for information only

b. Dose Adjustment

Use the minimum effective dose to establish and maintain a low iron burden.

It is recommended that serum ferritin be monitored every month and that the dose of TEVA-DEFERASIROX (TYPE J) be adjusted if necessary, every 3 to 6 months based on serum ferritin trends to minimize the risk of overchelation (see 7 WARNINGS AND PRECAUTIONS). Dose adjustments should be made in steps of 3.5 or 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The Liver Iron Concentration (LIC) should be assessed periodically by an appropriate method such as biopsy or MRI in order to verify treatment response. In patients with beta-thalassemia not adequately controlled with daily doses of 21 mg/kg, doses of up to 28 mg/kg may be considered. Doses of TEVA-DEFERASIROX (TYPE J) should not exceed 28 mg/kg per day since, with the exception of beta-thalassemia patients, there is limited experience with doses above this level (see 14 CLINICAL TRIALS).

As with other iron chelator treatment, the risk of toxicity of TEVA-DEFERASIROX (TYPE J) may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. If the serum ferritin falls below 1000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the dose is greater than 17.5 mg/kg/day (high doses despite body iron burden being in the target range or consistently below the target range is not recommended). Use the minimum effective dose to maintain iron burden in the target range. Continued administration of deferasirox in the 14-28 mg/kg/day range when the body iron burden is approaching or within the normal range has resulted in life threatening adverse events (see 7 WARNINGS AND PRECAUTIONS). Evaluate the need for ongoing chelation for patients whose conditions do not require regular blood transfusions.

If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with TEVA-DEFERASIROX (TYPE J).

B. Non-transfusion-dependent thalassemia syndromes

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) or serum ferritin consistently >800 mcg/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation. Doses should be in mg/kg and must be calculated and rounded to the nearest whole tablet size. TEVA-DEFERASIROX (TYPE J) is available in three strengths (90 mg, 180 mg and 360 mg).

a. Starting Dose

The recommended initial daily dose of TEVA-DEFERASIROX (TYPE J) is 7 mg/kg body weight.

b. Dose Adjustment

Use the minimum effective dose to establish and maintain a low iron burden.

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 7 WARNINGS AND PRECAUTIONS). Every 3 to 6 months of treatment, consider a dose increase in increments of 3.5 to 7 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 mcg/L and not showing a downward trend, and the patient is tolerating the drug well. The incidence of adverse effects increases with increasing dose. Experience with doses of 14mg/kg is limited. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 mcg/L, dosing should not exceed 7 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction is recommended to 7 mg/kg or less when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 mcg/L.

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 mcg/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

C. Transfusional iron overload and non-transfusion-dependent thalassemia syndromes

a. Dosing Considerations

Conversion from deferasirox dispersible tablets for oral suspension to deferasirox film-coated tablets: For patients who are currently on chelation therapy with deferasirox dispersible tablets and converting to deferasirox film-coated tablets, the dose of deferasirox film-coated tablets should be about 30% lower,

rounded to the nearest whole tablet. The table below provides additional information on dosing conversion to deferasirox film-coated tablets.

Table 2: Dosing Conversion from Deferasirox dispersible tablets to Deferasirox film-coated tablets

	Deferasirox dispersible tablets for oral suspension	Deferasirox film-coated tablets
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

Geriatrics (≥ 65 years of age): The pharmacokinetics of deferasirox have not been studied in geriatric patients. The dosing recommendations for elderly patients are the same as described above. In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

Pediatrics (2 to 16 years of age): The dosing recommendations for pediatric patients are the same as for adult patients. 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 7 WARNINGS AND PRECAUTIONS). In children < 6 years of age, exposure was about 50% lower than adults. Since dosing is individually adjusted according to response this difference in exposure is not expected to have clinical consequences. Changes in weight of pediatric patients over time must also be taken into account when calculating the dose.

Deferasirox has been associated with serious and fatal adverse reactions in pediatric patients in the postmarketing setting (see 7 WARNINGS AND PRECAUTIONS). These events were frequently associated with volume depletion or with continued deferasirox dispersible tablets doses in the 20-40 mg/kg/day range, equivalent to 14-28 mg/kg/day deferasirox film-coated tablets when body iron burden was approaching or in the normal range (patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended). The risk of toxicity of TEVA-DEFERASIROX (TYPE J) may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. Use the minimum effective dose to maintain iron burden in the target range.

Monitor renal and liver function more frequently in pediatric patients in the presence of renal toxicity risk factors, including episodes of dehydration, fever and acute illness that may result in volume depletion or decreased renal perfusion. Use the minimum effective dose. Interrupt TEVA-DEFERASIROX (TYPE J) in pediatric patients with transfusional iron overload and consider dose interruption in pediatric patients with non-transfusion-dependent iron overload, for acute illnesses which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal.

Evaluate the risk benefit profile of continued TEVA-DEFERASIROX (TYPE J) use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs.

Patients with renal impairment: Deferasirox has not been studied in patients with renal impairment (see 2 CONTRAINDICATIONS). In the setting of decreased renal function, evaluate the risk benefit profile of continued TEVA-DEFERASIROX (TYPE J) use. Use the minimum effective TEVA-DEFERASIROX (TYPE J) dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic therapies until improvement of renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt TEVA-DEFERASIROX (TYPE J) to prevent severe and irreversible renal injury.

For adult patients, the daily dose of TEVA-DEFERASIROX (TYPE J) should be reduced by 7 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes. In clinical trials with deferasirox, from those patients who underwent dose reduction, creatinine levels returned to baseline in only 25% of patients and in 60% of them, creatinine levels remained elevated >33% of the average pre-treatment levels. For pediatric patients, the dose should be reduced by 7 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits. A total of 6 patients < 16 years developed creatinine levels >ULN during the core phase of the registration studies. Dose reductions were performed in 5 patients, in 4 of whom the levels returned to baseline. Creatinine levels fell to < ULN in the fifth patient but remained higher than baseline.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, TEVA-DEFERASIROX (TYPE J) therapy should be interrupted (see 8.4 Abnormal Laboratory findings: Hematologic, Clinical chemistry and other quantitative data).

Patients with hepatic impairment: Deferasirox has been studied in a clinical trial in patients with hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50%. TEVA-DEFERASIROX (TYPE J) should not be used in patients with severe hepatic impairment (Child-Pugh C) (see 7 WARNINGS and PRECAUTIONS and 10 CLINICAL PHARMACOLOGY; Special Populations and Conditions). Deferasirox treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of normal range. The pharmacokinetics of deferasirox were not influenced by such transaminase levels. The treating physician should initiate treatment with a dose taking into account general dosing instructions together with the extent of hepatic impairment. Close monitoring of efficacy and safety parameters is recommended. It is recommended that serum transaminase, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is an unexplained, persistent, and progressive increase in serum transaminase levels, TEVA-DEFERASIROX (TYPE J) treatment should be interrupted.

Patients with skin rash: Skin rashes may occur during TEVA-DEFERASIROX (TYPE J) treatment. Severe skin rashes may require interruption of TEVA-DEFERASIROX (TYPE J) treatment.

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males. Since dosing is individually adjusted according to response this difference in clearance is not expected to have clinical consequences.

4.4 Administration

TEVA-DEFERASIROX (TYPE J) tablets should be swallowed whole once daily with water or other liquids, preferably at the same time each day. TEVA-DEFERASIROX (TYPE J) should be taken on an empty stomach or with a light meal (containing 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 with lettuce, tomato, and 1 packet mustard) (see 10 CLINICAL PHARMACOLOGY).

For patients who are unable to swallow whole tablets, TEVA-DEFERASIROX (TYPE J) tablets may be crushed and administered by sprinkling the full dose on a soft food (e.g, yogurt or applesauce). Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed and followed with a glass of water. The dose should not be stored for future use.

4.5 Missed Dose

If a dose is missed it should be taken as soon as remembered on that day, and the next dose should be taken as planned. Doses should not be doubled to make up for a missed dose.

5 OVERDOSAGE

In healthy volunteers, single doses of up to 40 mg/kg per day with the tablet for oral suspension formulation were 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. Standard procedures for management of overdose (e.g. induction of emesis or gastric lavage) may be indicated as well as symptomatic treatment, as medically appropriate.

In one pediatric case, a dose of 2-3 times the prescribed dose for six days resulted in acute renal failure requiring hemofiltration and acute liver injury/failure, which were reversible with intensive care support.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	Film-coated tablets / 90 mg, 180 mg, or 360 mg	The inactive ingredients are: core tablet: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, poloxamer, povidone; film-coating material: FD&C Blue #2/indigo carminine aluminum lake, hypromellose, polyethylene glycol, talc, titanium dioxide.

TEVA-DEFERASIROX (TYPE J) (deferasirox) film-coated tablets is available in three strengths: 90 mg, 180 mg and 360 mg.

- 90 mg: Light blue, ovaloid, biconvex, film-coated tablets with beveled edges, embossed with '90' on one side and plain on the other side.
- 180 mg: Medium blue, ovaloid, biconvex, film-coated tablets with beveled edges, embossed with '180' on one side and plain on the other side.
- 360 mg: Dark blue, ovaloid, biconvex, film-coated tablets with beveled edges, embossed with '360' on one side and plain on the other side.

TEVA-DEFERASIROX (TYPE J) (deferasirox) is supplied in blisters of 30 film-coated tablets (3 blisters of 10 tablets per box).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

The decision to remove accumulated iron should be individualized based on anticipated clinical benefits and risks of chelation therapy (see 4 DOSAGE AND ADMINISTRATION).

The safety of deferasirox when administered with other iron chelation therapy has not been established.

No studies on the effects of deferasirox on the ability to drive or use machines have been performed. Patients experiencing dizziness should exercise caution when driving or operating machinery.

Carcinogenesis and Mutagenesis

Carcinogenesis and Mutagenesis
See 16 NON-CLINICAL TOXICOLOGY; Mutagenicity and Carcinogenicity sections.

Cardiovascular

Deferasirox has not been studied in patients with acute cardiac failure due to iron overload. Therefore, the use of TEVA-DEFERASIROX (TYPE J) is not recommended in these patients.

Ear/Nose/Throat

Auditory disturbances (high-frequency hearing loss, decreased hearing) have been reported with deferasirox therapy (see 8 ADVERSE REACTIONS). Auditory testing is recommended before the start of TEVA-DEFERASIROX (TYPE J) treatment and thereafter at regular intervals.

The frequency of auditory adverse events irrespective of causality was increased among pediatric patients, who received deferasirox dispersible tablets doses greater than 25 mg/kg/day equivalent to 17.5 mg/kg/day deferasirox when serum ferritin was less than 1,000 mcg/L (patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended; see 4 DOSAGE AND ADMINISTRATION).

Gastrointestinal

Gastrointestinal irritation may occur during TEVA-DEFERASIROX (TYPE J) treatment. Upper gastrointestinal (GI) ulceration and haemorrhage and upper and lower GI perforations have been reported uncommonly in patients, including children and adolescents, receiving deferasirox. There have been rare reports of fatal GI haemorrhages and perforations. Fatal haemorrhages have been reported more frequently in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients and there have been reports of ulcers complicated with gastrointestinal perforation (see 8 ADVERSE REACTIONS). Physicians and patients should remain alert for signs and

symptoms of GI ulceration, perforation and haemorrhage during TEVA-DEFERASIROX (TYPE J) therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected.

Caution should be exercised in patients who are taking TEVA-DEFERASIROX (TYPE J) in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and in patients receiving anticoagulants (see 9 DRUG INTERACTIONS).

Hematologic

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure (see 8.5 Post-Market Adverse Drug Reactions). The relationship of these episodes to treatment with deferasirox is unknown. In line with the standard clinical management of such hematological disorders, complete blood count (CBC) should be available at baseline and blood counts should be monitored regularly during therapy. Dose interruption of treatment with TEVA-DEFERASIROX (TYPE J) should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with TEVA-DEFERASIROX (TYPE J) may be considered, once the cause of the cytopenia has been elucidated.

Hepatic/Biliary/Pancreatic

TEVA-DEFERASIROX (TYPE J) is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see 4.1 Dosing Considerations and 10 CLINICAL PHARMACOLOGY; Special Populations and Conditions). Elevations of serum transaminase levels (greater than 5 times the upper limit of normal) have been observed in 40 patients (6.1%; 40/652) receiving deferasirox in the context of 4 registration studies. In these patients, the transaminase levels were already >5*ULN at baseline in 6 of the 40 patients. In 25 of the 40 patients, the transaminase levels at baseline were above the upper limit of normal but less than 5*ULN.

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials.

In a 5-year pediatric observational study, single events of elevations in ALT and AST suspected to be related to deferasirox were reported in 21.1% and 11.9%, respectively. Approximately 12% of patients on study required a dose reduction or interruption of deferasirox to manage the increase in transaminases and 2.7% of patients discontinued treatment.

There have been post-marketing reports of hepatic failure in patients treated with deferasirox. There are a total of 24 international reports of hepatic failure – 21 post-marketing reports and 3 reports from clinical studies. Two of the 24 cases were reported in Canada. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients. As of the cut-off date above, no patient with normal baseline liver function or without additional life-threatening complications of their underlying disease has developed hepatic failure.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is an unexplained, persistent and progressive increase in serum transaminase levels, TEVA-DEFERASIROX (TYPE J) treatment should be interrupted.

Acute liver injury and failure, including fatal outcomes, have occurred in pediatric deferasirox-treated patients. Liver failure occurred in association with acute kidney injury in pediatric patients at risk for over chelation during a volume depleting event. Interrupt TEVA-DEFERASIROX (TYPE J) therapy when acute liver injury or acute kidney injury is suspected and during volume depletion. Monitor liver and renal function more frequently in pediatric patients who are receiving TEVA-DEFERASIROX (TYPE J) in the 14-28 mg/kg/day range and when iron burden is approaching normal. Use the minimum effective dose to achieve and maintain a low iron burden (see 4 DOSAGE AND ADMINISTRATION).

In the clinical trial and post-marketing settings, cases of serious acute pancreatitis were observed with and without documented underlying biliary conditions. A causal association to deferasirox could not be ruled out.

Immune

Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see 8.5 Post-Market Adverse Reactions). If hypersensitivity reactions occur, TEVA-DEFERASIROX (TYPE J) should be discontinued and appropriate medical intervention instituted. TEVA-DEFERASIROX (TYPE J) should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

Monitoring and Laboratory Tests

Monitor renal function more frequently in patients with pre-existing renal disease or decreased renal function. Monitor liver and renal function more frequently during volume depletion and in patients receiving TEVA-DEFERASIROX (TYPE J) in the 14-28 mg/kg/day range when iron burden is approaching the normal range (see 4 DOSAGE AND ADMINISTRATION).

Serum Ferritin: Serum ferritin should be measured monthly to assess response to therapy and to evaluate for the possibility of overchelation of iron, although the correlation coefficient between serum ferritin and liver iron content (LIC) was 0.63, and changes in serum ferritin levels may not always reliably reflect changes in LIC. If the serum ferritin falls consistently below 500 mcg/L, temporary interruption of TEVA-DEFERASIROX (TYPE J) therapy should be considered (see 4 DOSAGE AND ADMINISTRATION). Closer monitoring of serum ferritin levels, as well as renal and hepatic function is recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. Dose reduction may be considered to avoid overchelation.

As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately given to patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see 4 DOSAGE AND ADMINISTRATION).

Renal: Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose and during therapy. It is recommended that serum creatinine and creatinine clearance be assessed twice before initiating therapy. Weekly monitoring of serum creatinine and creatinine clearance is recommended in the first month after initiation or modification of therapy, and monthly thereafter. Tests for proteinuria should be performed monthly (see Renal section below).

Hepatic: It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see Hepatic/Biliary/Pancreatic section above).

Hematologic: In line with the standard clinical management of such hematological disorders, complete blood count (CBC) should be available at baseline and blood counts should be monitored regularly during therapy. Dose interruption of treatment with TEVA-DEFERASIROX (TYPE J) should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with TEVA-DEFERASIROX (TYPE J) may be considered, once the cause of the cytopenia has been elucidated (see Hematologic section above).

Auditory: Auditory disturbances (high-frequency hearing loss, decreased hearing) have been reported with deferasirox therapy (see 8 ADVERSE REACTIONS).

Auditory testing is recommended before the start of TEVA-DEFERASIROX (TYPE J) treatment and thereafter at regular intervals.

Ophthalmologic: Ocular disturbances (lens opacities, early cataracts, maculopathies) have been reported with deferasirox therapy (see 8 ADVERSE REACTIONS). Ophthalmic testing (including fundoscopy) is recommended before the start of TEVA-DEFERASIROX (TYPE J) treatment and thereafter at regular intervals.

Renal

Deferasirox has not been studied in patients with renal impairment. Deferasirox treatment has been initiated only in patients with serum creatinine within the age-appropriate normal range and therefore must be used with caution in patients with elevated serum creatinine levels (see 2 CONTRAINDICATIONS).

Deferasirox-treated patients experienced dose-dependent increases in serum creatinine. Increases in creatinine that were > 33% at ≥ 2 consecutive post baseline visits occurred at a greater frequency in deferasirox-treated patients compared to deferoxamine-treated patients (38% vs. 14%, respectively) in study 0107. In these beta-thalassemia patients, 94% of the creatinine elevations remained within the normal range. Under the dose adjustment instructions, dose reduction was required in one third of patients showing serum creatinine increase. In most patients undergoing dose reductions serum creatinine levels did not return to baseline; in 60% of patients undergoing dose reduction, serum creatinine remained elevated at > 33% without progression (see 8.4 Abnormal laboratory findings: Hematologic, clinical chemistry and other quantitative data).

TEVA-DEFERASIROX (TYPE J) can cause acute kidney injury. Pre-existing renal disease and concomitant use of other nephrotoxic drugs may increase the risk of acute kidney injury in adult and pediatric patients. An analysis of pediatric patients treated with deferasirox dispersible tablets in pooled clinical trials (n=158)

found a higher rate of renal adverse events among patients receiving doses greater than 25 mg/kg/day, equivalent to 17.5 mg/kg/day deferasirox, while their serum ferritin values were less than 1,000 mcg/L (patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended; (see 4 DOSAGE AND ADMINISTRATION). The risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. Use the minimum dose to establish and maintain a low iron burden (see 4 DOSAGE AND ADMINISTRATION). Acute illnesses associated with volume depletion and overchelation may increase the risk of acute kidney injury in pediatric patients. In pediatric patients, small decreases in estimated glomerular filtration rate (eGFR) can result in increases in deferasirox exposure, particularly in younger patients with body surface area typical of patients less than age 7 years. This can lead to a cycle of worsening renal function and further increases in deferasirox exposure, unless the dose is reduced or interrupted.

Cases of acute renal failure (some with fatal outcome) have been reported following the post-marketing use of deferasirox. There have been rare cases of acute renal failure requiring dialysis. For the fatal cases, it is impossible to completely exclude a contributory role of deferasirox to the renal impairment, although the fatalities in these critically ill patients could be attributable to other underlying diseases. The fact that there was an improvement after stopping the treatment in most of the cases with non-fatal acute renal failure is suggestive of a contributory role of deferasirox to these cases (see 8.5 Post Market Adverse Reactions).

Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose and during therapy. It is recommended that serum creatinine and creatinine clearance be assessed twice before initiating therapy. Weekly monitoring of serum creatinine and creatinine clearance is recommended in the first month after initiation or modification of therapy, and monthly thereafter. Patients with pre-existing renal conditions or patients who are receiving medicinal products that may depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients (see 4.1 Dosing Considerations). In pediatric patients, interrupt TEVA-DEFERASIROX (TYPE J) during acute illnesses which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor renal function more frequently. Promptly correct fluid deficits to prevent renal injury. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Dose reduction, interruption, or discontinuations should be considered for elevations in serum creatinine (see 8.4 Abnormal laboratory findings: Hematologic, clinical chemistry and other quantitative data).

Renal tubulopathy has been reported in patients treated with deferasirox. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 mcg/L.

Tests for proteinuria should be performed monthly. As needed, additional markers of renal tubular function (e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria) may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, TEVA-DEFERASIROX (TYPE J) should be interrupted (see 4 DOSAGE AND ADMINISTRATION).

Skin

Serious skin reactions: Severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity vasculitis, as well as drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life - threatening or fatal, and rare cases of erythema multiforme, have occurred during treatment with deferasirox. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. Upon suspicion of any SCAR, TEVA-DEFERASIROX (TYPE J) should be discontinued immediately and should not be reintroduced.

Skin rashes: skin rashes may also appear during TEVA-DEFERASIROX (TYPE J) treatment. For rashes of mild to moderate severity, TEVA-DEFERASIROX (TYPE J) may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, TEVA-DEFERASIROX (TYPE J) may be re-introduced after resolution of the rash, at a lower dose followed by gradual dose escalation.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies conducted in pregnant women. No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see 16 NON-CLINICAL PHARMACOLOGY; Reproductive and Developmental Toxicology). The potential risk for humans is unknown. It is therefore recommended that TEVA-DEFERASIROX (TYPE J) should not be used during pregnancy. Patients taking oral contraceptives may be at risk of getting pregnant because TEVA-DEFERASIROX (TYPE J) may decrease the efficacy of hormonal contraceptives (see 9 DRUG INTERACTIONS).

7.1.2 Breast-feeding

It is not known whether deferasirox is excreted in human milk. In an animal study, deferasirox and its metabolites were present in breast milk of rats following a 10 mg/kg oral dose. The concentration of deferasirox was approximately 20-fold higher in maternal milk than in maternal plasma 4-8 hours post dose (see16 NON-CLINICAL PHARMACOLOGY; Reproductive and Developmental Toxicology). Therefore, women should be advised against breast-feeding while taking TEVA-DEFERASIROX (TYPE J).

7.1.3 Pediatrics (2 to 16 years of age):

There are limited data on the safety and effectiveness of deferasirox in pediatric patients aged 2 to 5 (see 14 CLINICAL TRIALS). Deferasirox has not been associated with growth retardation in children followed for up to 5 years in clinical studies. However, as a precautionary measure, body weight and longitudinal growth in pediatric patients should be monitored at regular intervals (every 12 months), see 1.1 Pediatrics.

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) with transfusional hemosiderosis received deferasirox, there were no unexpected safety findings observed regarding adverse events or laboratory abnormalities with the exception of an increase in single events of elevated transaminases suspected to be related to deferasirox: 21.1% and 11.9% of pediatric patients had elevated

alanine aminotransferase (ALT) and aspartate aminotransferase, respectively. Within the range of the known safety profile, increases in serum creatinine of >33% and above the upper limit of normal (ULN) on ≥2 consecutive occasions were observed in 3.1% of children and elevation of ALT greater than 5 times the ULN on ≥2 consecutive occasions was reported in 4.3% of children.

Of the 242 patients who had pre-and post-baseline eGFR measurements, 116 (48%) patients had a decrease in eGFR of ≥33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days. Adverse events leading to permanent discontinuation from the study included liver injury (n=11), renal tubular disorder (n=1), proteinuria (n=1), hematuria (n=1), upper gastrointestinal hemorrhage (n=1), vomiting (n=2), abdominal pain (n=1), and hypokalemia (n=1).

An analysis of pediatric patients treated with deferasirox dispersible tablets in pooled clinical trials (n=158) found a higher rate of renal adverse events among patients receiving doses greater than 25 mg/kg/day, equivalent to 17.5 mg/kg/day deferasirox, while their serum ferritin values were less than 1,000 mcg/L (patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended; see 4 DOSAGE AND ADMINISTRATION).

Deferasirox has been associated with serious and fatal adverse reactions in pediatric patients in the postmarketing setting. These events were frequently associated with volume depletion or with continued deferasirox dispersible tablets doses in the 20-40 mg/kg/day range, equivalent to 14-28 mg/kg/day deferasirox, when body iron burden was approaching or in the normal range (patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended; see 4 DOSAGE AND ADMINISTRATION).

Monitor renal and liver function more frequently in pediatric patients in the presence of renal toxicity risk factors, including episodes of dehydration, fever and acute illness that may result in volume depletion or decreased renal perfusion. Use the minimum effective dose.

Interrupt TEVA-DEFERASIROX (TYPE J) in pediatric patients with transfusional iron overload and consider dose interruption in pediatric patients with non-transfusion-dependent iron overload, for acute illnesses which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal.

Evaluate the risk benefit profile of continued TEVA-DEFERASIROX (TYPE J) use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs.

7.1.4 Geriatrics (≥ 65 years of age):

Four hundred and thirty-one (431) patients ≥ 65 years of age have been studied in clinical trials of deferasirox. The majority of these patients had myelodysplastic syndrome (MDS, n= 393; ß-thalassemia, n= 2; other anemias, n= 36). In general, caution should be used in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy. In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients

and should be monitored closely for adverse reactions that may require a dose adjustment, see 1.2 Geriatrics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Over 7000 patients have been treated with deferasirox in clinical studies as of October 31, 2011. In the initial registration program, 652 patients were treated with deferasirox in therapeutic studies lasting for a median of 366 days in pediatric and adult patients (52 patients between 2 and 5 years of age, 240 patients between 6 and 16 years of age, 330 patients between 17 to 65 years of age and 30 patients ≥ 65 years). These 652 patients included 421 with β-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 302 were male and 456 were Caucasian. In the sickle cell disease population, 89% of patients were black.

The most frequently occurring adverse events (all causalities) in the therapeutic trials of deferasirox were diarrhea, vomiting, nausea, headache, constipation, dyspepsia, abdominal pain, pyrexia, cough, proteinuria, increases in serum creatinine and transaminases, pruritis and skin rash. Gastrointestinal disorders, increases in serum creatinine and skin rash were dose related. Adverse events which most frequently led to dose interruption, dose adjustment, or discontinuation of therapy were skin rash, gastrointestinal disorders, infections, increased creatinine, and increased transaminases.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

In clinical trials in patients with transfusional iron overload, the most frequent reactions reported during chronic treatment with deferasirox in adult and pediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain), and skin rash in about 7% of patients. Mild, non-progressive, dose-dependent increases in serum creatinine occurred in 34% of patients (see 8.4 Abnormal laboratory findings: Hematologic, clinical chemistry and other quantitative data).

In clinical trials in patients with transfusional iron overload, elevations of liver transaminases as suspected drug-related adverse events were reported in about 2% of patients. The increases in liver transaminases were not dose-dependent. Forty percent of these patients had elevated levels (above the upper limit of normal) prior to receiving deferasirox. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). High frequency hearing loss and lenticular opacities (early cataracts) have been observed in <1% of patients treated with deferasirox (see 7 WARNINGS AND PRECAUTIONS, Ear/Nose/Throat and Gastrointestinal).

In a 1-year, randomized, double-blind, placebo-controlled study in patients with non-transfusion-dependent thalassemia syndromes, the most frequently reported AEs in the deferasirox 10 mg/kg/day

group (at least 10%) were headache (16.4%), upper respiratory tract infection (14.5%), oropharyngeal pain (10.9%), pyrexia (10.9%), and rash (10.9%). Table 4 displays adverse events occurring in >5% of deferasirox -treated patients.

Table 4: Adverse Events Occurring in >5% of deferasirox-treated Patients in Study A2209

	Deferasirox	Deferasirox	Placebo	Placebo	Placebo
	5 mg/kg/day	10 mg/kg/day	5 mg/kg/day	10 mg/kg/day	Any dose
	N=55	N=55	N=28	N=28	N=56
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	**42 (76.4)**	**43 (78.2)**	**20 (71.4)**	**25 (89.3)**	**45 (80.4)**
Headache	2 (3.6)	9 (16.4)	4 (14.3)	4 (14.3)	8 (14.3)
Upper respiratory tract infection	7 (12.7)	8 (14.5)	5 (17.9)	6 (21.4)	11 (19.6)
Oropharyngeal pain	4 (7.3)	6 (10.9)	0	2 (7.1)	2 (3.6)
Pyrexia	6 (10.9)	6 (10.9)	5 (17.9)	3 (10.7)	8 (14.3)
Rash	2 (3.6)	6 (10.9)	1 (3.6)	2 (7.1)	3 (5.4)
Diarrhea	3 (5.5)	5 (9.1)	2 (7.1)	4 (14.3)	6 (10.7)
Fatigue	1 (1.8)	5 (9.1)	2 (7.1)	2 (7.1)	4 (7.1)
Nausea	4 (7.3)	5 (9.1)	1 (3.6)	6 (21.4)	7 (12.5)
Abdominal pain	2 (3.6)	4 (7.3)	1 (3.6)	3 (10.7)	4 (7.1)
Anaemia	3 (5.5)	4 (7.3)	0	2 (7.1)	2 (3.6)
Nasopharyngitis	5 (9.1)	4 (7.3)	2 (7.1)	3 (10.7)	5 (8.9)
Rhinitis	1 (1.8)	4 (7.3)	1 (3.6)	0	1 (1.8)
Abdominal pain upper	3 (5.5)	3 (5.5)	0	0	0
Dyspepsia	0	3 (5.5)	0	0	0
Gastroenteritis	1 (1.8)	3 (5.5)	0	2 (7.1)	2 (3.6)
Influenza	3 (5.5)	3 (5.5)	1 (3.6)	0	1 (1.8)
Insomnia	1 (1.8)	3 (5.5)	2 (7.1)	0	2 (3.6)

In Study 2209, one patient in the placebo 10 mg/kg group experienced an ALT increase to >5 x ULN and >2 x baseline (Table 5). Three deferasirox-treated patients (all in the 10 mg/kg group) had 2 consecutive serum creatinine level increases >33% from baseline and >ULN. Serum creatinine returned to normal in all patients (in one spontaneously and in the other two after drug interruption).

Table 5: Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 2209

Laboratory Parameter	Deferasirox 5 mg/kg (N=55) n (%)	Deferasirox 10 mg/kg (N=55) n (%)	Placebo 5 mg/kg (N=28) n (%)	Placebo 10 mg/kg (N=28) n (%)	Placebo (N=56) n (%)
Serum Creatinine					
Creatinine increase (>33% from baseline and >ULN at ≥2 consecutive post-baseline values)	0 (0.0)	3 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)
SGPT/ALT					
SGPT/ALT (>5 x ULN and >2 x baseline)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.8)

A total of 652 patients were treated with deferasirox in therapeutic studies of adult and pediatric patients with β-thalassemia (n=421), rare anemias (n=99) and sickle cell disease (n=132). This population was 46% male, 70% Caucasian and included 292 patients ≤16 years of age. In the sickle cell disease population, 89% of patients were black. A total of 94% of β-thalassemia patients, 70% of patients with rare anemias, and 86% of patients with sickle cell disease patients received therapy for ≥ 48 weeks.

The data in Table 6 displays the adverse events, regardless of causality, occurring in >5% of patients in either treatment group in the primary efficacy study 0107 in which 296 β-thalassemia patients were treated with deferasirox and 290 patients received deferoxamine as an active comparator. Adverse events which most frequently led to dose interruption, dose adjustment, or discontinuation of therapy were skin rash, gastrointestinal disorders, infections, increased creatinine, and increased transaminases (see 8.4 Abnormal laboratory findings: Hematologic, clinical chemistry and other quantitative data). Discontinuations due to adverse events with a suspected relationship to deferasirox occurred in 7 patients.

Table 6: Adverse Events Occurring in >5% of β-thalassemia Patients in the Comparative Trial

Preferred Term	Deferasirox N=296 n (%)	Deferoxamine N=290 n (%)
Pyrexia	56 (18.9)	69 (23.8)
Headache	47 (15.9)	59 (20.3)
Abdominal pain	41 (13.9)	28 (9.7)
Cough	41 (13.9)	55 (19.0)
Nasopharyngitis	39 (13.2)	42 (14.5)
Diarrhea	35 (11.8)	21 (7.2)
Creatinine increased[1]	33 (11.1)	0 (0)
Influenza	32 (10.8)	29 (10.0)
Nausea	31 (10.5)	14 (4.8)
Pharyngolaryngeal pain	31 (10.5)	43 (14.8)

Preferred Term	Deferasirox N=296 n (%)	Deferoxamine N=290 n (%)
Vomiting	30 (10.1)	28 (9.7)
Respiratory tract infection	28 (9.5)	23 (7.9)
Bronchitis	27 (9.1)	32 (11.0)
Rash	25 (8.4)	9 (3.1)
Abdominal pain upper	23 (7.8)	15 (5.2)
Pharyngitis	23 (7.8)	30 (10.3)
Arthralgia	22 (7.4)	14 (4.8)
Acute tonsillitis	19 (6.4)	15 (5.2)
Fatigue	18 (6.1)	14 (4.8)
Rhinitis	18 (6.1)	22 (7.6)
Back pain	17 (5.7)	32 (11.0)
Ear infection	16 (5.4)	7 (2.4)
Urticaria	11 (3.7)	17 (5.9)
[1] >33% increase compared to average baseline values		

The data in Table 7 displays the adverse events, regardless of causality, occurring in >1% in the pooled β-thalassemia patients by dose administered. The most frequently reported adverse events were abdominal pain, pyrexia and headache. In the 30 mg/kg dose group, the most frequently reported adverse events were abdominal pain, diarrhea and increased serum creatinine. Skin rash and ALT increase were the only adverse events that resulted in discontinuation.

Table 7: Most frequently reported AEs (>1% of all patients) – pooled β-thalassemia patients by dose administered

Preferred term	Deferasirox 10 mg/kg N=143	Deferasirox 20 mg/kg N=106	Deferasirox 30 mg/kg N=172	All patients N=421
	Total	Total	Total	Total
	n (%)	n (%)	n (%)	n (%)
Abdominal pain	38 (26.6)	21 (19.8)	41 (23.8)	100 (23.8)
Pyrexia	47 (32.9)	31 (29.2)	20 (11.6)	98 (23.3)
Headache	37 (25.9)	20 (18.9)	26 (15.1)	83 (19.7)
Cough	38 (26.6)	17 (16.0)	25 (14.5)	80 (19.0)
Diarrhea	24 (16.8)	9 (8.5)	37 (21.5)	70 (16.6)
Nasopharyngitis	23 (16.1)	16 (15.1)	20 (11.6)	59 (14.0)
Vomiting	28 (19.6)	12 (11.3)	18 (10.5)	58 (13.8)
Rash	12 (8.4)	10 (9.4)	30 (17.4)	52 (12.4)
Nausea	11 (7.7)	11 (10.4)	28 (16.3)	50 (11.9)
Creatinine increased[1]	2 (1.4)	13 (12.3)	34 (19.8)	49 (11.6)
Laryngeal pain	20 (14.0)	12 (11.3)	17 (9.9)	49 (11.6)
Pharyngitis	28 (19.6)	9 (8.5)	10 (5.8)	47 (11.2)
Influenza	19 (13.3)	12 (11.3)	13 (7.6)	44 (10.5)

Preferred term	Deferasirox 10 mg/kg N=143	Deferasirox 20 mg/kg N=106	Deferasirox 30 mg/kg N=172	All patients N=421
	Total	Total	Total	Total
	n (%)	n (%)	n (%)	n (%)
Rhinitis	28 (19.6)	8 (7.5)	6 (3.5)	42 (10.0)
URTI[2]	9 (6.3)	8 (7.5)	24 (14.0)	41 (9.7)
Bronchitis	7 (4.9)	9 (8.5)	20 (11.6)	36 (8.6)
Arthralgia	13 (9.1)	8 (7.5)	13 (7.6)	34 (8.1)
Back pain	9 (6.3)	16 (15.1)	9 (5.2)	34 (8.1)
Constipation	9 (6.3)	6 (5.7)	12 (7.0)	27 (6.4)
Fatigue	7 (4.9)	6 (5.7)	13 (7.6)	26 (6.2)
Ear infection	13 (9.1)	7 (6.6)	3 (1.7)	23 (5.5)
Tonsillitis	8 (5.6)	7 (6.6)	6 (3.5)	21 (5.0)
Post procedural pain	2 (1.4)	8 (7.5)	10 (5.8)	20 (4.8)
Acute tonsillitis	2 (1.4)	6 (5.7)	11 (6.4)	19 (4.5)
Asthenia	8 (5.6)	7 (6.6)	4 (2.3)	19 (4.5)
Gastroenteritis	8 (5.6)	6 (5.7)	5 (2.9)	19 (4.5)
Chest pain	2 (1.4)	8 (7.5)	8 (4.7)	18 (4.3)
Ear pain	3 (2.1)	5 (4.7)	4 (2.3)	12 (2.9)
Palpitations	1 (0.7)	4 (3.8)	7 (4.1)	12 (2.9)
Tachycardia	5 (3.5)	4 (3.8)	3 (1.7)	12 (2.9)
Transfusion reaction	7 (4.9)	3 (2.8)	2 (1.2)	12 (2.9)
Urticaria	3 (2.1)	4 (3.8)	5 (2.9)	12 (2.9)
Dyspepsia	4 (2.8)	3 (2.8)	4 (2.3)	11 (2.6)
Pain in extremity	5 (3.5)	3 (2.8)	3 (1.7)	11 (2.6)
Pruritus	3 (2.1)	4 (3.8)	4 (2.3)	11 (2.6)
Rhinorrhoea	1 (0.7)	6 (5.7)	3 (1.7)	10 (2.4)
Sinusitis	0	6 (5.7)	4 (2.3)	10 (2.4)
Transaminases increased	8 (5.6)	1 (0.9)	1 (0.6)	10 (2.4)
Urinary tract infection	2 (1.4)	1 (0.9)	7 (4.1)	10 (2.4)
Herpes simplex	3 (2.1)	1 (0.9)	5 (2.9)	9 (2.1)
Otitis media	2 (1.4)	1 (0.9)	6 (3.5)	9 (2.1)
Toothache	2 (1.4)	3 (2.8)	4 (2.3)	9 (2.1)
Anxiety	3 (2.1)	2 (1.9)	3 (1.7)	8 (1.9)
Bone pain	1 (0.7)	1 (0.9)	6 (3.5)	8 (1.9)
Conjunctivitis	6 (4.2)	1 (0.9)	1 (0.6)	8 (1.9)
Dyspnoea	0	2 (1.9)	6 (3.5)	8 (1.9)
Muscle cramp	1 (0.7)	0	7 (4.1)	8 (1.9)
Productive cough	4 (2.8)	3 (2.8)	1 (0.6)	8 (1.9)
Tooth abscess	2 (1.4)	0	6 (3.5)	8 (1.9)
Abdominal distension	1 (0.7)	0	6 (3.5)	7 (1.7)
Cholelithiasis	2 (1.4)	1 (0.9)	4 (2.3)	7 (1.7)
Enteritis	5 (3.5)	1 (0.9)	1 (0.6)	7 (1.7)
Epistaxis	4 (2.8)	1 (0.9)	2 (1.2)	7 (1.7)

Preferred term	Deferasirox 10 mg/kg N=143	Deferasirox 20 mg/kg N=106	Deferasirox 30 mg/kg N=172	All patients N=421
	Total	Total	Total	Total
	n (%)	n (%)	n (%)	n (%)
Erythema	3 (2.1)	2 (1.9)	2 (1.2)	7 (1.7)
Hypoacusis	4 (2.8)	2 (1.9)	1 (0.6)	7 (1.7)
Insomnia	0	3 (2.8)	4 (2.3)	7 (1.7)
Vertigo	2 (1.4)	4 (3.8)	1 (0.6)	7 (1.7)
Alanine aminotransferase increased	4 (2.8)	2 (1.9)	0	6 (1.4)
Cardiac murmur	0	0	6 (3.5)	6 (1.4)
Depression	0	2 (1.9)	4 (2.3)	6 (1.4)
Dizziness	1 (0.7)	2 (1.9)	3 (1.7)	6 (1.4)
Dysmenorrhoea	0	3 (2.8)	3 (1.7)	6 (1.4)
Lymphadenopathy	2 (1.4)	1 (0.9)	3 (1.7)	6 (1.4)
Myalgia	1 (0.7)	1 (0.9)	4 (2.3)	6 (1.4)
Pharyngitis streptococcal	3 (2.1)	3 (2.8)	0	6 (1.4)
Proteinuria	1 (0.7)	1 (0.9)	4 (2.3)	6 (1.4)
Rash maculo-papular	0	3 (2.8)	3 (1.7)	6 (1.4)
Seasonal allergy	0	1 (0.9)	5 (2.9)	6 (1.4)
Abdominal discomfort	1 (0.7)	0	4 (2.3)	5 (1.2)
Contusion	2 (1.4)	0	3 (1.7)	5 (1.2)
Cystitis	1 (0.7)	1 (0.9)	3 (1.7)	5 (1.2)
Frequent bowel movements	1 (0.7)	1 (0.9)	3 (1.7)	5 (1.2)
Oedema peripheral	0	2 (1.9)	3 (1.7)	5 (1.2)
Respiratory tract infection	1 (0.7)	1 (0.9)	3 (1.7)	5 (1.2)
Syncope	2 (1.4)	2 (1.9)	1 (0.6)	5 (1.2)
Viral infection	1 (0.7)	1 (0.9)	3 (1.7)	5 (1.2)

[1] >33% increase compared to average baseline values
[2] Upper respiratory tract infection

Pooled Analysis of Pediatric Clinical Trial Data

A nested case control analysis was conducted within a deferasirox pediatric pooled clinical trial dataset to evaluate the effects of dose and serum ferritin level, separately and combined, on kidney function. Among 1213 children (aged 2 to 15 years) with transfusion-dependent thalassemia, 162 cases of acute kidney injury (eGFR <90 ml/min/1.73m^2) and 621 matched-controls with normal kidney function (eGFR >120 ml/min/1.73m^2) were identified. The primary findings were:

- A 26% increased risk of acute kidney injury was observed with each 5 mg/kg increase in daily deferasirox dispersible tablets dosage equivalent to 3.5 mg/kg deferasirox, starting at 20 mg/kg/day equivalent to 14 mg/kg/day deferasirox (95%CI: 1.08-1.48).
- A 25% increased risk for acute kidney injury was observed with each 250 mcg/L decrease in serum ferritin starting at 1250 mcg/L (95%CI: 1.01-1.56).

- Among pediatric patients with a serum ferritin <1000 mcg/L, those who received deferasirox dispersible tablets dosage >30 mg/kg/day equivalent to 21 mg/kg/day deferasirox compared to those who received lower dosages, had a higher risk for acute kidney injury (OR=4.47, 95%CI: 1.25-15.95), consistent with overchelation.

In addition, a cohort based analysis of adverse events was conducted in the deferasirox pediatric pooled clinical trial data. Pediatric patients who received deferasirox dispersible tablets dose >25 mg/kg/day, equivalent to 17.5 mg/kg/day deferasirox, when their serum ferritin was <1000 mcg/L (n = 158; patients received high doses despite body iron burden being in the target range or consistently below the target range which is not recommended; see 4 DOSAGE AND ADMINISTRATION)- had a 6-fold greater rate of renal adverse events (IRR = 6.00, 95% CI: 1.75-21.36) and a 2-fold greater rate of dose interruptions (IRR = 2.06, 95% CI: 1.33-3.17) compared to the time-period prior to meeting these simultaneous criteria. Adverse events of special interest (cytopenia, renal, hearing, and gastrointestinal disorders) occurred 1.9-fold more frequently when these simultaneous criteria were met, compared to preceding time-periods (IRR = 1.91, 95% CI: 1.05-3.48).

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The less common adverse events which occurred in clinical trials and considered to be related to deferasirox are listed below.

Cardiovascular: QT prolongation[1]

General disorders: Pyrexia, oedema, fatigue

Ear and labyrinth disorders: Deafness

Eye disorders: Cataract, maculopathy, optic neuritis

Gastrointestinal: Duodenal ulcer, gastric ulcer (including multiple ulcers) gastritis, gastrointestinal haemorrhage, oesophagitis

Hepatic/Biliary/Pancreatic: Cholelithiasis, hepatitis, acute pancreatitis[2]

Nervous system: Dizziness

Psychiatric disorders: Anxiety, sleep disorder

Renal and urinary disorders: Renal tubular disorder (Fanconi syndrome)

Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain

Skin and subcutaneous tissue disorders: Pigmentation disorder, erythema multiforme.

1. Three cases of QT interval prolongation were reported in the clinical trials, however, a causal relationship to study drug was not established.
2. Cases of serious acute pancreatitis were observed with and without documented underlying biliary conditions.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In the comparative study 0107, 113 patients treated with deferasirox had non-progressive increases in serum creatinine > 33% above baseline (Table 8). Twenty-five (25) patients required dose reductions. Increases in serum creatinine appeared to be dose-related. Of the 17 patients with elevations in SGPT/ALT levels > 5 times the ULN at consecutive visits, one discontinued deferasirox therapy. One patient experienced increases in transaminases to >10x ULN which normalized upon drug discontinuation but then increased sharply upon rechallenge. Increases in transaminases did not appear to be dose-related and most of these patients had elevated transaminases prior to receiving deferasirox therapy.

Table 8: Number (%) of patients with increases in SGPT/ALT or serum creatinine in Study 0107

Laboratory parameter	Deferasirox N=296 n (%)	Deferoxamine N=290 n (%)
Serum creatinine		
No. patients with creatinine > 33% and <ULN at ≥ 2 consecutive post-baseline visits	106 (35.8)	40 (13.8)
No. patients with creatinine increase > 33% and >ULN at ≥ 2 consecutive post-baseline visits	7 (2.4)	1 (0.3)
SGPT/ALT		
No. patients with SGPT/ALT >5 x ULN at ≥2 post-baseline visits	8 (2.7)	2 (0.7)
No. patients with SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	17 (5.7)	5 (1.7)

A total of 652 patients were treated with deferasirox in clinical studies 107, 108, and 109. Of these patients, 237 (36%) had an increase in serum creatinine >33% on at least 2 consecutive visits, 68 (11%) of whom underwent dose reduction. The remainder returned to serum creatinine <33% above baseline without dose reduction. Of the 68 patients who underwent dose reduction, 17 (25%) returned to normal, 41 (60%) remained elevated at >33% without progression and the remaining 10 (15%) fluctuated between baseline and 33%.

Based on limited data in patients with sickle cell disease (N=132) and other rare anemias (N=99), the type and frequency of adverse events observed were similar to those observed in patients with β-thalassemia. The adverse event profile in patients <16 years of age was similar to that seen in adults, regardless of disease state.

In 49 adult β-thalassemia patients treated for greater than 1 year and up to 3 years, the type and frequency of adverse events was similar to that seen in patients treated for up to 1 year.

8.5 Post-Market Adverse Reactions

Spontaneously reported adverse reactions, presented below, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Since the International Birth Date (November 2, 2005), the cumulative exposure to marketed deferasirox is 123,619 patient-years as of October 31, 2011.

Renal and urinary disorders

Cases of acute renal failure (some with fatal outcome) have been reported following the post-marketing use of deferasirox. Rarely biopsy proven interstitial nephritis has also been reported. Acute renal failure (mostly serum creatinine increases ≥ 2x upper limit of normal, and usually reversible after treatment interruption), hematuria, renal tubular necrosis, and Renal tubulopathy has been reported in patients treated with deferasirox. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 mcg/L.

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).

Immune system disorders
Hypersensitivity reactions (including anaphylaxis and angioedema)

Gastrointestinal disorders
Duodenal ulcer, gastric ulcer, gastrointestinal bleeding, and gastrointestinal perforation

Blood and lymphatic system disorders
Agranulocytosis, neutropenia, thrombocytopenia and aggravated anemia

Hepatic/Biliary/Pancreatic

Hepatic failure

Hypocalcemia has been reported to occur during deferasirox therapy.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Use with other iron chelator: The safety of deferasirox when administered with other iron chelation therapy has not been established.

Use with Aluminum Containing Antacid Preparations: The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, TEVA-DEFERASIROX (TYPE J) should not be taken with aluminum-containing antacid preparations (see 7 WARNINGS AND PRECAUTIONS).

Use with Agents Metabolised through CYP3A4: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17%. In the clinical setting, this effect may be more pronounced. Therefore, caution should be exercised when TEVA-DEFERASIROX (TYPE J) is combined with substances metabolised through CYP3A4 (e.g. cyclosporine, simvastatin, hormonal contraceptive agents), due to a possible decrease in efficacy.

Use with Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension at single dose of 30 mg/kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of TEVA-DEFERASIROX (TYPE J) with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy. If TEVA-DEFERASIROX (TYPE J) and a potent UGT inducer are used concomitantly, increases in the dose of TEVA-DEFERASIROX (TYPE J) should be considered based on clinical response to therapy.

Use with Bile Acid Sequestrants: In a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox tablets for oral suspension resulted in a 45% decrease in deferasirox exposure (AUC).

Use with Agents Metabolized by CYP2C8: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension at 30 mg/kg/day for 4 days) and the CYP2C8 substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide AUC and C_{max} by 131% and 62%, respectively. When TEVA-DEFERASIROX (TYPE J) and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between TEVA-DEFERASIROX (TYPE J) and other CYP2C8 substrates like paclitaxel cannot be excluded.

Use with Agents Metabolized by CYP1A2: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension (at a repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. When TEVA-DEFERASIROX (TYPE J) and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between TEVA-DEFERASIROX (TYPE J) and other CYP1A2 substrates such as clozapine and tizanidine may be possible.

Use with busulfan: Based on Literature reports, concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC). The AUC increase ranged approximately 40 to 150%. The mechanism of the interaction remains unclear. Caution should be exercised when TEVA-DEFERASIROX (TYPE J) is combined with busulfan and the patient's plasma concentrations of busulfan should be monitored.

Use with Digoxin: In healthy volunteers, deferasirox tablets for oral suspension had no effect on the pharmacokinetics of digoxin. The effect of digoxin on deferasirox pharmacokinetics has not been studied.

Use with Vitamin C: The concomitant administration of deferasirox tablets and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg were allowed in clinical studies without negative consequences. High doses of vitamin C should not be used.

Use with ulcerogenic potential drugs: Concomitant administration of TEVA-DEFERASIROX (TYPE J) with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of TEVA-DEFERASIROX (TYPE J) in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see 7 WARNINGS AND PRECAUTIONS).

Use with hydroxyurea: The interaction of deferasirox with hydroxyurea has not been formally studied. No inhibition of deferasirox metabolism by hydroxyurea is expected based on the results of an *in vitro* study.

9.5 Drug-Food Interactions

Exposure (C_{max}) of deferasirox tablets was increased when taken with a high-fat meal (see 10 CLINICAL PHARMACOLOGY). TEVA-DEFERASIROX (TYPE J) should be taken on an empty stomach or with a light meal, preferably at the same time each day (see 4 DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions between deferasirox and gallium contrast media have not been studied. It is known that the results of gallium-67 imaging may be distorted by the iron chelator deferoxamine due to chelation of gallium-67. It is therefore recommended that TEVA-DEFERASIROX (Type J) therapy be interrupted at least five days before gallium-67 scintigraphy.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Deferasirox is an orally active chelator that is highly selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although its highest affinity is for iron, deferasirox has a significant affinity for aluminum. Deferasirox has very low affinity for zinc and copper, and 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.

10.2 Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study with deferasirox tablets for oral suspension formulation of 10, 20 and 40 mg/kg/day was able to induce net iron excretion (0.119, 0.329 and 0.445 mg Fe/kg body weight/d, respectively) within the clinically relevant range (0.1 to 0.5 mg Fe/kg/day). Iron excretion was predominantly fecal.

Daily treatment with deferasirox (tablets for oral suspension) at doses of 20 and 30 mg/kg for one year in frequently transfused adult and pediatric patients with beta-thalassemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about 0.4 and 8.9 mg Fe/g liver (biopsy dry weight) on average, respectively, and serum ferritin was reduced by about 36 and 926 mcg/L on average, respectively. At these same doses the ratios of iron excretion: iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. Deferasirox (tablets for oral suspension) induced similar responses in iron-overloaded patients with other anemias. Daily doses of 10 mg/kg for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions.

Cardiac Electrophysiology: The effect of 20 and 40 mg/kg of deferasirox (tablets for oral suspension) on QT interval was evaluated in a single-dose, double-blind, randomized, placebo-and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female volunteers aged 18 to 65 years. No evidence of prolongation of the QTc interval was observed in this study; however, the relevance of this study to long-term deferasirox use is unknown.

In patients with non-transfusion-dependent thalassemia syndromes and iron overload, treatment with deferasirox (tablets for oral suspension) at a dose of 10 mg/kg/day for one year led to a reduction in mean liver iron concentration from baseline by -3.80 mg Fe/g dw, while an increase of 0.38 mg Fe/g dw was observed in patients treated with placebo. In addition, treatment with deferasirox at a dose of 10 mg/kg/day for one year led to a reduction in mean serum ferritin from baseline by -222.0 mcg/L, while an increase of 114.5 mcg/L was observed in patients treated with placebo.

In patients with cardiac iron deposition (MRI T2* <20 ms), treatment with deferasirox (tablets for oral suspension) was shown to remove cardiac iron as demonstrated by progressive improvements in T2* values over 3 years of observation. In patients without cardiac deposition, deferasirox was shown to prevent clinically relevant cardiac iron deposition (maintenance of T2* at >20 ms) up to 1 year of observation, despite significant ongoing transfusion exposure.

10.3 Pharmacokinetics

Deferasirox tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the tablet for oral suspension formulation. After strength-adjustment, the deferasirox tablet formulation (i.e., 360 mg strength) had comparable bioavailability to the tablet for oral suspension formulation (i.e., 500 mg strength) with respect to the mean area under the plasma concentration time

curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI 20.3% to 40.0%), however a clinical exposure/response analysis revealed no effects of clinical relevance.

Absorption: Based on studies in patients with the tablet for oral suspension, deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. In healthy volunteers, the deferasirox tablet formulation showed comparable t_{max}. The C_{max} and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3 to 2.3 after multiple doses with the tablet for oral suspension formulation.

The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. Bioavailability of deferasirox in deferasirox tablets was 36% greater than with deferasirox dispersible tablets for oral suspension.

A food-effect study involving administration of the deferasirox tablets to healthy volunteers under fasting conditions and with a light (i.e., a whole wheat English muffin with jelly and a glass of skim milk) or high-fat (fat content >50% of calories) meal indicated that the AUC and C_{max} were slightly decreased after a light meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased by 18% and 29%, respectively. The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that TEVA-DEFERASIROX (TYPE J) should be taken on an empty stomach or with a light meal (see 4 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 is 14.37 ± 2.69 L in adults.

Metabolism: Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No evidence for induction or inhibition of CYP450 enzymes (CYP1A1, CYP1A2 and CYP2D6) at therapeutic doses has been observed. No inhibition of deferasirox metabolism by hydroxyurea was observed in an in vitro study. Deferasirox undergoes enterohepatic recycling.

Elimination: 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 to16 hours following oral administration.

Special Populations and Conditions

- **Pediatrics:** The overall exposure of deferasirox in young children (aged 2 to 5) was about 50% lower than in adults and this age group may require higher maintenance doses than are necessary in adults (see 4 DOSAGE AND ADMINISTRATION; 7.1.3 Pediatrics).

- **Geriatrics:** The pharmacokinetics of deferasirox have not been studied in geriatric patients. Caution is advised in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy. Appropriate dose adjustment and monitoring is essential as clinical trials suggest, a higher frequency of adverse reactions in elderly patients than younger patients (see 4 DOSAGE AND ADMINISTRATION; 7.1.4 Geriatrics).

- **Sex:** Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males (see 4 DOSAGE AND ADMINISTRATION).

- **Hepatic Insufficiency:** The average AUC of deferasirox in 6 subjects with mild hepatic impairment (Child-Pugh A) increased 16% over that found in 6 subjects with normal hepatic function, while the average AUC of deferasirox in 6 subjects with moderate hepatic impairment (Child-Pugh B) increased 76% over that found in 6 subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment increased 22% over that found in subjects with normal hepatic function (see 7 WARNINGS AND PRECAUTIONS and 4.1 Dosing Considerations). Efficacy of deferasirox was not studied in this pharmacokinetic investigation of subjects with hepatic impairment.

- **Renal Insufficiency:** Deferasirox has not been studied in patients with renal impairment. Monitoring of renal function is advised before initiating therapy or increasing the dose and during therapy (see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION, 7 WARNING AND PRECAUTION; Renal).

11 STORAGE AND STABILITY

Store between 15°C-30°C, protect from moisture. Store in original container.

Keep in a safe place out of the reach of children and pets.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

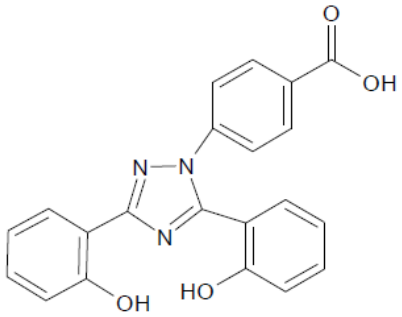
Proper name: Deferasirox

Chemical name: 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4]-triazole-1-yl]benzoic acid

Molecular formula: $C_{21}H_{15}N_3O_4$

Molecular mass: 373.36 g/mol

Structural formula:



Physicochemical properties: A white to light yellow powder.

Solubility: Soluble in Dimethyl sulfoxide, in Dimethylformamide and is insoluble in water.

14 CLINICAL TRIALS

The following information is based on clinical trials conducted with deferasirox tablets for oral suspension. Deferasirox tablets contain the same active ingredient as deferasirox dispersible tablets for oral suspension; however, the exposure is 30% higher in the deferasirox tablets. Currently, there are no clinical trial data in patients administered deferasirox tablets; however, deferasirox tablets have been evaluated in healthy volunteer trials.

14.1 Clinical Trials by Indication

β-thalassemia and transfusional hemosiderosis

Study 0107, was a 1-year, multi-centre, open-label, randomized, Phase III, active comparator control study to compare deferasirox tablets for oral suspension and deferoxamine in patients with β-thalassemia and transfusional hemosiderosis. Patients ≥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/kg once daily or subcutaneous DESFERAL®[1](deferoxamine) at starting doses of 20 to 60 mg/kg for at least 5 days per week based on LIC (liver iron concentration) at baseline (2 to 3, >3 to 7, >7 to 14 and >14 mg Fe/g dry weight (dw)). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dw were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol. Consequently, the ratio of deferasirox tablets for oral suspension to deferoxamine doses for the two lower LIC categories was disproportionately low (1:4) compared to the two upper LIC categories (1:2). A total of 586 patients were randomized and treated (including 154 patients <16 years of age and received either deferasirox tablets for oral suspension (296 patients) or deferoxamine (290 patients). There were no major differences in the baseline demographic characteristics between the groups. In both groups more than 97% of patients had received prior chelation therapy. Approximately two-thirds of each group was heavily iron overloaded as evidenced by an LIC value > 7 mg Fe/g dw at baseline.

Chronic anemias and transfusional hemosiderosis

Study 0108 was an open-label, non-comparative, phase II trial of efficacy and safety of deferasirox tablets for oral suspension given for 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine. Similar to Study 0107, patients received 5, 10, 20, or 30 mg/kg per day of deferasirox tablets for oral suspension based on baseline LIC. A total of 184 patients (adult and pediatric) were treated in this study: 85 patients with β-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other, n=22). Nineteen percent (N=35) of patients were <16 years of age (11 patients were ≥ 2 - < 6 years, 11 patients were 6 - < 12 years, and 13 patients were 12 - < 16 years) and 16% (N=30) of patients were ≥ 65 years of age. Thirty-seven patients had not received prior chelation therapy.

Sickle cell disease and transfusional hemosiderosis

Study 0109 was a 1-year, open-label, randomized, Phase II, active comparator control study to compare deferasirox tablets for oral suspension and deferoxamine in patients with sickle cell disease and

[1] PrDESFERAL® is a registered trademark

transfusional hemosiderosis. As in Study 0107, patients received 5, 10, 20, or 30, mg/kg per day of deferasirox tablets for oral suspension or subcutaneous deferoxamine at doses of 20 to 60 mg/kg for 5 days per week based on baseline LIC. The primary objective of this study was safety and tolerability of deferasirox in this patient population. The population examined in study 0109 was adult and pediatric patients with sickle cell disease and chronic iron overload from repeated blood transfusions. This population included individuals receiving intermittent or regular transfusions. A total of 195 patients were randomized to receive either deferasirox tablets for oral suspension (132 patients) or deferoxamine (63 patients) with the following distribution by age group: 7 patients were 2-< 6 years; 45 patients were 6 - < 12 years; 46 patients were 12 - <16 years; 96 patients were ≥ 16 years. There were no major differences in the patient populations randomized to receive either deferasirox or deferoxamine with regard to baseline demographics and disease characteristics. In both groups about 60% of patients had received prior chelation therapy. A somewhat higher percentage of deferasirox patients were heavily iron overloaded (LIC value > 7 mg Fe/g dw) at baseline when compared with deferoxamine (deferasirox 64%; deferoxamine 49%).

Relevant demographic characteristics for these studies are shown in **Table 9** and **Table 10**.

Table 9: Summary of patient demographics for clinical trials in chronic iron overload

Study #	Trial design	Dosage, route of administration and duration	Study patients (n=number)	Mean age ± SD (Range)	Gender M/F
0107	open-label, randomized, Phase III, active comparator control study	Deferasirox tablets for oral suspension by baseline LIC: 5, 10, 20, or 30 mg/kg DFO by baseline LIC‡: 20-30, 25-35, 35-50, >50 mg/kg Duration: 52 weeks	Deferasirox =296 DFO =290	17.2 ± 9.71 (2-53)	282 (48.1%) / 304 (51.9%)
0108	open-label, non-comparative, phase II trial of efficacy and safety	Deferasirox tablets for oral suspension by baseline LIC: 5, 10, 20, or 30 mg/kg Duration: 52 weeks	Deferasirox =184	35.0 ± 22.4 (3-81)	93 (50.5%) / 91 (49.5%)
0109	open-label, randomized, Phase II, active comparator control study	Deferasirox tablets for oral suspension by baseline LIC: 5, 10, 20, or 30 mg/kg DFO by baseline LIC: 20-30, 25-35, 35-50, >50 mg/kg Duration: 52 weeks (ongoing)	Deferasirox =132 DFO =63	19.2 ± 10.9 (3-54)	80 (41.0%) / 115 (59.0%)

Study #	Trial design	Dosage, route of administration and duration	Study patients (n=number)	Mean age ± SD (Range)	Gender M/F
‡LIC: liver iron concentration SD: standard deviation DFO: deferoxamine					

Table 10: Number and % of patients treated with deferasirox by study (n=652)

Deferasirox patients	Study 106 N = 40	Study 107 N = 296	Study 108 N = 184	Study 109 N = 132	All patients N = 652
Patients < 16 years	36 (90%)	154 (52%)	35 (19%)	67 (51%)	292 (45%)
Age group					
≥ 2 - < 6 years	7 (17.5%)	30 (10.1%)	11 (6.0%)	4 (3.0%)	52 (8.0%)
6 - < 12 years	13 (32.5%)	67 (22.6%)	11 (6.0%)	30 (22.7%)	121 (18.6%)
12 - < 16 years	16 (40.0%)	57 (19.3%)	13 (7.1%)	33 (25.0%)	119 (18.3%)
16 - < 50 years	4 (10.0%)	142 (48.0%)	99 (53.8%)	63 (47.7%)	308 (47.2%)
50 - < 65 years	0	0	20 (10.9%)	2 (1.5%)	22 (3.4%)
≥ 65 years	0	0	30 (16.3%)	0	30 (4.6%)

Study results

In the primary efficacy study 0107, treatment duration was 12 months. LIC, an accepted indicator of total body iron burden, was assessed at baseline and after 12 months of therapy by liver biopsy or non-invasively by biomagnetic susceptometry. Success rate, the primary efficacy endpoint, was defined as a reduction in LIC of ≥ 3 mg Fe/g dw for baseline values ≥ 10 mg Fe/g dw, reduction of baseline values between 7 and < 10 to < 7 mg Fe/g dw, or maintenance or reduction for baseline values <7 mg Fe/g dw. Deferasirox was to be declared non-inferior to deferoxamine if the lower limit of the 95% confidence interval (two-sided) of the difference in success rates was above -15%.

Table 11: Success rates for Study 0107 (reduction or maintenance of LIC according to baseline and non-inferiority to deferoxamine)

	Deferasirox	DFO
Biopsy & SQUID	**n=276**	**n=277**
Success rate (n (%))	146 (52.9)	184 (66.4)
95% CI	[47.0, 58.8]	[60.9, 72.0]
Difference and 95% CI	-13.5 [-21.6, -5.4]	
LIC < 7 mg Fe/g dw	**n=85**	**n=87**
Success rate (n (%))	34 (40.0)	72 (82.8)
95% CI	[29.6, 50.4]	[74.8, 90.7]
Difference [95% CI]	-42.8 [-55.9, -29.7]	
LIC ≥ 7 mg Fe/g dw	**n=191**	**n=190**
Success rate (n (%))	112 (58.6)	112 (58.9)
95% CI	[51.7, 65.6]	[52.0, 65.9]
Difference [95% CI]	-0.3 [-10.2, 9.6]	

DFO: deferoxamine

The primary efficacy population consisted of 553 patients (deferasirox n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an AE. Of these 553 patients, 56 patients were < 6 years; 130 patients were 6 - < 12 years; 106 patients were 12 - <16 years; 261 patients were ≥ 16 years and <65 years. The overall success rates were 52.9% for deferasirox and 66.4% for deferoxamine with a difference of -13.5 in success rates and a 95% CI of [-21.6, -5.4]. Non-inferiority to deferoxamine was not achieved because the lower limit of the CI was below -15%. However, non-inferiority was demonstrated in a group of patients with baseline LIC levels ≥ 7 mg Fe/g dw who were allocated to the higher dose groups (deferasirox tablets for oral suspension) doses of 20 or 30 mg/kg and deferoxamine doses of ≥ 35 mg/kg. The success rates with deferasirox and deferoxamine were 58.6% and 58.9%, respectively, and the lower limit of the 95% CI (-10.2%) was above the non-inferiority threshold of -15% (see **Table 11**).

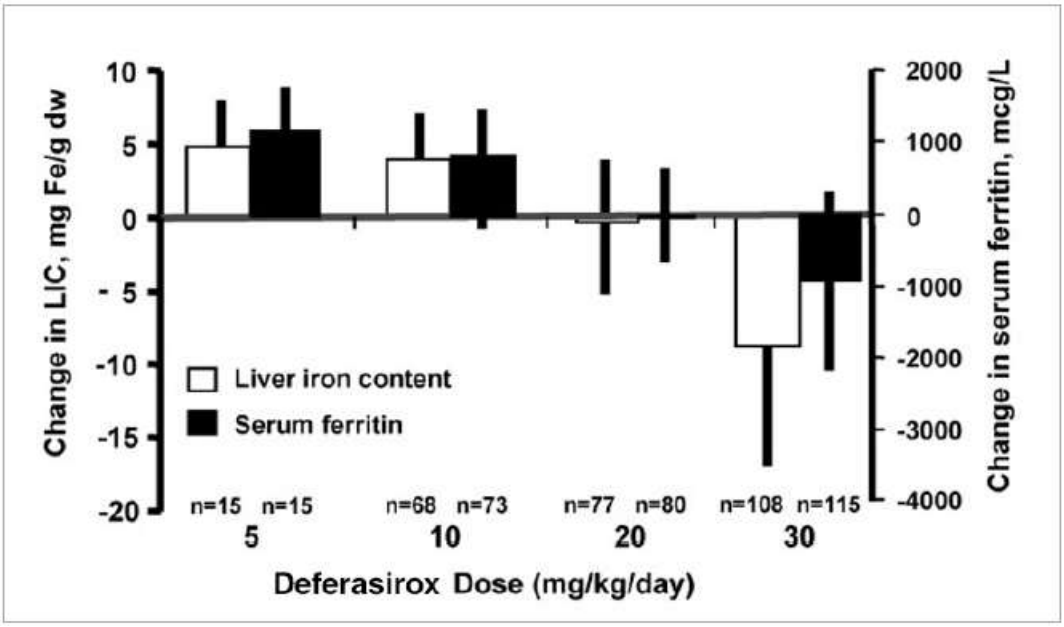
In patients with LIC ≥ 7 mg Fe/g dw who were treated with deferasirox tablets for oral suspension 20 to 30 mg/kg per day a statistically significant reduction in LIC from baseline was observed (-5.3 ± 8.0 mg Fe/g dw, p<0.001, t-test) which was not statistically significantly different from deferoxamine (-4.3 ± 5.8 mg Fe/g dw, p = 0.367).

Table 12: Ratio of iron excretion/iron intake and change in serum ferritin levels from baseline to 1 year of treatment in the primary efficacy Study 0107

Protocol Recommended Dose (mg/kg/day)		Mean actual prescribed dose (mg/kg/day)		Ratio of iron excretion/iron intake		Serum ferritin levels (mcg/L) Mean change from baseline ± SD	
Defera-sirox tablets for oral suspension	Deferox-amine	Defera-sirox tablets for oral suspension	Deferox-amine	Deferasirox tablets for oral suspension Mean ± SD (n)	Deferoxamine Mean ± SD (n)	Deferasirox tablets for oral suspension Mean ± SD (n)	Deferoxamine Mean ± SD (n)
5	20-30	6.2 ± 1.6	33.9 ± 9.9	0.58 ± 0.328 (15)	0.95 ± 0.101 (13)	+1189± 700 (15)	+211 ± 459 (13)
10	25-35	10.2 ± 1.2	36.7 ± 9.2	0.67 ± 0.365 (68)	0.98 ± 0.217 (75)	+833 ± 817 (73)	+32 ± 585 (77)
20	35-50	19.4 ± 1.7	42.4 ± 6.6	1.02 ± 0.398 (77)	1.13 ± 0.241 (87)	-36 ± 721 (80)	-364 ± 614 (89)
30	≥50	28.2 ± 3.5	51.6 ± 5.8	1.67 ± 0.716 (108)	1.44 ± 0.596 (98)	-926 ± 1416 (115)	-1003 ± 1428 (101)
SD: standard deviation							

Reduction of LIC and serum ferritin were observed with deferasirox tablets for oral suspension doses of 20 to 30 mg/kg. Deferasirox tablets for oral suspension doses below 20 mg/kg/day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg/kg/day of TEVA-DEFERASIROX (TYPE J) tablets for oral suspension is recommended (see 4 DOSAGE AND ADMINISTRATION).

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox (5 to 30 mg/kg per day) in Study 107



The results of the primary efficacy study are supported by the second major efficacy study, study 0108. The primary endpoint was to demonstrate a success rate significantly greater than 50% with deferasirox. In the total population, the success rate (50.5%) was not statistically significantly higher than 50%. However, in patients with LIC ≥ 7 mg Fe/g dw for whom both baseline and end of study LIC was available and who received deferasirox tablets for oral suspension 20 to 30 mg/kg per day, the success rate was 58.5% [p=0.022 (50.3, 66.6)] and there was a statistically significant reduction in the absolute LIC from baseline to end of study (-5.5 ± 7.4 mg Fe/g dw, $p < 0.001$, t-test). There was also a dose dependent effect on serum ferritin and the ratio of iron excretion to iron intake from doses of 5 to 30 mg/kg per day.

The primary objective of study 0109 was safety and tolerability (see 8 ADVERSE REACTIONS). A total of 132 patients were treated with deferasirox and 63 patients with deferoxamine. At the time of the 6-month interim analysis, dose-dependent increases in the ratio of iron excretion to iron intake from doses of 5 to 30 mg/kg per day of deferasirox tablets for oral suspension were observed. At the end of the study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least one post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

In an analysis of 192 beta-thalassemia patients dose escalated up to a maximum dose of 40 mg/kg/day of deferasirox tablets for oral suspension (treated for up to 32 weeks), a further decrease in serum ferritin of 11.9% was observed (from the start of dosing >30 mg/kg/day). This was based on a pooled analysis of patients who were exposed to doses greater than 30 mg/kg/day of deferasirox tablets for oral suspension in the key registration trials and their ongoing long-term extensions (Studies 0107/E, 0108/E, and 0109/E), and in another large clinical trial and its ongoing long-term extension (2402/E).

A cardiac sub-study was conducted as part of a Phase IV study. The cardiac sub-study was a one year, prospective, open-label, single-arm study which included two cohorts of severely iron overloaded β-thalassemia patients with LVEF values ≥56%: 114 patients with baseline T2* values >5 to <20 ms indicating myocardial siderosis (treatment cohort) and 78 patients with myocardial T2* ≥20 ms indicating no clinically significant cardiac iron deposition (prevention cohort). In the treatment cohort, the deferasirox tablets for oral suspension starting dose was 30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. In the prevention cohort, the deferasirox tablets for oral suspension starting dose was 20-30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. The primary endpoint of the cardiac sub-study was the change in T2* at one year. In the treatment cohort, T2* (geometric mean ± coefficient of variation) significantly increased from a baseline value of 11.2 ms ± 40.5% to 12.9 ms ± 49.5%, representing a significant improvement of 16% (p <0.0001). In the treatment cohort, improvement in T2* was observed in 69.5% of patients and stabilization of T2* in 14.3% of patients. LVEF remained stable and within the normal range: 67.4 ± 5.7% to 67.1 ± 6.0%. In the prevention cohort, myocardial T2* remained within the normal range and was unchanged from a baseline value of 32.0 ms ± 25.6% to 32.5 ms ± 25.1% (+2%; p = 0.565) indicating that daily treatment with deferasirox can prevent cardiac iron loading in β-thalassemia patients with a history of high transfusion exposure, and regular, ongoing transfusions.

Patients in the treatment cohort of the 1-year core study had the option to participate in two 1-year extensions. Over a three-year treatment duration period, there was a statistically significant (p<0.0001), progressive improvement in the geometric mean of cardiac T2* from baseline overall, in the severe cardiac iron overload sub-group, which is associated with a high risk of cardiac failure (T2* >5 to <10 ms), and in the mild to moderate cardiac iron overload sub-group (T2* 10 to <20 ms) (Table 13). Using the geometric mean ratio, the T2* increase was 43% above baseline in all patients, 37% increase from baseline in the T2* >5 to <10 ms sub-group, and 46% increase from baseline in the T2* 10 to <20 ms sub-group. Continuous treatment with deferasirox tablets for oral suspension for up to 3 years at doses >30 mg/kg/day effectively reduced cardiac iron in thalassemia major patients with myocardial siderosis as shown by the number of patients who normalized their T2* or improved to a category associated with a lower risk of cardiac failure (Table 14).

Table 13: Geometric mean of T2* (ms) at baseline, and at the end of year 1, 2, and 3

Baseline cardiac T2* sub-group	Baseline (year 0)	End of core (year 1)	End of E1 (year 2)	End of E2 (year 3)
Overall	11.20 (n=105)	12.9(n=105) (p<0.0001)	14.79 (n=95) (p<0.0001)	17.12 (n=68) (p<0.0001)
T2* >5 to <10 ms	7.39 (n=41)	8.15 (n=41)	8.71 (n=35)	10.53 (n=24)
T2* 10 to <20 ms	14.62 (n=64)	17.39 (n=64)	20.13 (n=60)	22.32 (n=44)

E1 = end of first year extension
E2 = end of second year extension

Table 14: Transition table of cardiac T2* from core baseline to end of E2 (year 3)

Baseline cardiac T2* sub-group	Baseline n (%)	<5 ms n (%)	5 - <10 ms n (%)	10 - <20 ms n (%)	≥20 ms n (%)	Missing n (%)
>5 - <10 ms (N=39)	39 (100.0)	1 (2.6)	18 (46.2)	15 (38.5)	1 (2.6)	4 (10.3)
10 - <20 ms	62		4 (6.5)	16 (25.8)	40 (64.5)	2 (3.2)

Baseline cardiac T2* sub-group	Baseline n (%)	<5 ms n (%)	5 - <10 ms n (%)	10 - <20 ms n (%)	≥20 ms n (%)	Missing n (%)
(N=62)	(100.0)					
All patients (N=101)	101 (100.0)	1 (1.0)	22 (21.8)	31 (30.7)	41 (40.6)	6 (5.9)

A randomized, double-blind, placebo-controlled study to compare deferasirox tablets for oral suspension and placebo was conducted in patients with non-transfusion-dependent thalassemia syndromes and iron overload. Patients ≥10 years of age were enrolled in the study in a 2:1:2:1 randomization to receive either deferasirox tablets for oral suspension 5 mg/kg/day or deferasirox 10 mg/kg/day or matching placebo.

Transfusion independency of the patients was confirmed by the fact that blood transfusions 6 months prior to study start were not allowed and patients were excluded if a regular transfusion program was anticipated during the study. Iron overload was diagnosed by a serum ferritin >300 mcg/L at screening (two consecutive values at least 14 days apart from each other) and LIC ≥5 mg Fe/g dw measured by R2 MRI at screening. All patients with non-transfusion-dependent thalassemia syndromes were allowed with the exception of patients with HbS-variants or those whose clinical condition allowed phlebotomy.

In total, 166 patients were randomized. Demographics were well balanced. The main underlying disease was beta-thalassemia intermedia in 95 (57.2%) patients and HbE beta-thalassemia in 49 (29.5%) patients. The primary efficacy endpoint of change in liver iron concentration (LIC) from baseline to Week 52 was statistically significant in favor of both deferasirox treatment groups compared with placebo (Table 15). Furthermore, a statistically significant dose effect of deferasirox tablets for oral suspension was observed in favor of the 10 mg/kg/day dose.

Table 15: Primary efficacy analysis – Analysis of covariance of absolute change in liver iron concentration (mg Fe/g dw) between baseline and Week 52 (Full Analysis Set)

	Deferasirox tablets for oral suspension 5 mg/kg/day (N=55)	Deferasirox tablets for oral suspension 10 mg/kg/day (N=55)	Placebo (N=56)
Change from baseline			
Number of evaluable patients	51	54	54
Least squares mean	-1.95	-3.80	0.38
Standard error	0.500	0.484	0.486
95% confidence interval	-2.94, -0.96	-4.76, -2.85	-0.59, 1.34
Difference of deferasirox - Placebo			
Least squares mean	-2.33	-4.18	-
Standard error	0.700	0.687	-
95% confidence interval (1)	-3.89, -0.76	-5.71, -2.64	-
p-value (2)	0.001	<.001	-
Difference of deferasirox 10 mg/kg - deferasirox 5			

	Deferasirox tablets for oral suspension 5 mg/kg/day (N=55)	Deferasirox tablets for oral suspension 10 mg/kg/day (N=55)	Placebo (N=56)
mg/kg			
Least squares mean	-	-1.85	-
Standard error	-	0.695	-
95% confidence interval	-	-3.22, -0.48	-
p-value (3)	-	0.009	-

Estimates were obtained from an ANCOVA model for change in LIC between baseline and Week 52 with treatment as factor and baseline LIC as covariate.
(1) two-sided simultaneous confidence intervals using Dunnett's adjustment
(2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in LIC is not greater under deferasirox than under placebo. Critical alpha-level: 0.025
(3) two-sided p-value testing the hypothesis that the change in LIC is identical in the two deferasirox groups. Critical alpha-level: 0.05
The last available post-baseline LIC was carried forward if no LIC value was available at Week 52.
Only patients with both baseline and at least one post-baseline LIC value were included for this analysis.

The primary efficacy result was supported by additional analyses which showed a clear dose-response effect; this was reflected by a greater percentage of patients with an LIC decrease of ≥3 mg Fe/g dw in the 10 mg/kg/day deferasirox tablets for oral suspension group compared to the 5 mg/kg/day deferasirox group (56.4% versus 32.7%, respectively). In addition, a reduction of ≥30% in LIC between baseline and Week 52 was reported in approximately twice as many patients in the 10 mg/kg/day deferasirox tablets for oral suspension group (49.15%) compared to the 5 mg/kg/day deferasirox tablets for oral suspension group (25.5%). After one year of treatment, 27.3% of patients in the 10 mg/kg/day deferasirox tablets for oral suspension group and 14.5% of patients in the 5 mg/kg/day deferasirox tablets for oral suspension group achieved an LIC of < 5mg Fe/g dw.

In the deferasirox treated groups, three pregnancies were reported among 45 female patients of child-bearing potential; one of these occurred despite concomitant oral contraceptive use. Deferasirox may decrease the efficacy of hormonal contraceptives (see 9 DRUG INTERACTIONS).

14.2 Study Results

Comparative Bioavailability Studies

The bioavailability of deferasirox tablets was compared to that of deferasirox dispersible tablets for oral solution in a randomized, two-way, comparative bioavailability study in 32 healthy adult male and female subjects. Single doses of deferasirox were administered as 1080 mg (3 x 360 mg) tablets swallowed whole with water, or as 1500 mg (3 x 500 mg) deferasirox dispersible tablets, which were dispersed in a glass of water. The results of the study demonstrated similar values for AUC_T for the two dosage forms; however, C_{max} was 30% higher for the tablets as compared to deferasirox dispersible tablets for oral solution.

Table 16: Summary table of the comparative bioavailability data

Deferasirox (3 x 360 mg test vs. 3 x 500 mg reference) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (mcmol·h/L)	1273.78 1373.16 (43.94)	1270.79 1411.76 (48.82)	100	93.2-107.8
AUC_I (mcmol·h/L)	1307.04 1409.05 (44.17)	1327.01 1477.77 (49.17)	98	91.6-105.9
C_{max} (mcmol/L)	105.83 109.67 (27.63)	81.54 85.71 (31.86)	130	120.3-140.0
T_{max}§ (h)	2.00 (1.50-6.03)	3.00 (1.00-8.00)		
$T_{½}$€ (h)	13.039 (30.37)	16.278 (28.91)		

* Deferasirox 360 mg tablet

† Deferasirox 500 mg dispersible tablet for oral solution

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

14.3 Comparative Bioavailability Studies

A randomized, double-blinded, two-treatment, two-period, two-sequence, single dose, crossover, comparative bioavailability study of TEVA-DEFERASIROX (TYPE J) 360 mg film-coated tablets and JADENU® (deferasirox) 360 mg film-coated tablets (Novartis Pharmaceuticals Canada Inc.) was conducted in healthy, adult human subjects (N=28) under fasting conditions. The results are summarized in the table below:

Table 17: Summary table of the comparative bioavailability data

Deferasirox (1 x 360 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (mcg·h/mL)	206.18 214.10 (27.4)	216.54 228.34 (31.8)	95.2	89.0 - 101.9
AUC_I (mcg·h/mL)	210.46 218.44 (27.2)	220.19 232.11 (31.7)	95.6	89.4 - 102.2
C_{max} (mcg/mL)	19.20 19.81 (26.3)	19.45 20.12 (25.1)	98.7	92.5 - 105.3
T_{max}[3] (h)	3.50 (1.50 - 5.50)	3.00 (2.00 - 6.00)		
$T_{1/2}$[4] (h)	12.45 (29.9)	11.46 (21.7)		

[1] Teva-Deferasirox (TYPE J) (deferasirox) film-coated tablets, 360 mg (Teva Canada Limited)
[2] [Pr]JADENU® (deferasirox) film-coated tablets, 360 mg (Novartis Pharmaceuticals Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity Studies

Single oral doses of deferasirox tablets for oral suspension at 1000 mg/kg in mice and ≥ 500 mg/kg in rats resulted in mortality/morbidity. Single intravenous doses of deferasirox in mice resulted in mortality at 150 mg/kg. No mortality was observed in rats at the highest intravenous dose tested, 75 mg/kg.

Subacute Toxicity Studies

Mortality was observed at doses ≥ 200 mg/kg and at 100 mg/kg in the 2-week and 4-week rat study, respectively. Decreased tissue iron and changes in hematological parameters characteristic of a potent iron chelator were evident. Histopathologic findings of renal cortical tubular cytoplasmic vacuolation and gastrointestinal tract were common to both studies. Decreased hematopoiesis in the spleen, and splenic lymphoid depletion was observed after two weeks of administration. All effects were reversible following a non-dosing phase. In a rat exploratory studies in which rats were iron overloaded or received diet supplemented with iron or findings were limited to pharmacological effects on tissue/serum iron levels.

In 2 and 4-week studies in marmosets, decreased tissue iron levels was observed at all doses of deferasirox. Effects on hematopoiesis were evident at 400 mg/kg after 2-weeks of administration and at 130 mg/kg after 4-weeks of treatment, vacuolar degeneration of the renal cortical tubules at doses ≥ 200 mg/kg and at 130 mg/kg in the 2-week and 4-week study, respectively. Vacuolation of intrahepatic bile duct cells and marked inflammation of gall bladder epithelium with fibrosis of the gall bladder wall and vacuolar hyperplasia of the epithelium was noted in a single animal at 130 mg/kg after 4 weeks treatment. All effects were reversible following a non-dosing phase. In a two week exploratory study in marmosets preloaded with iron, no deferasirox related effects were observed. Dietary iron supplementation of marmosets did not reduce deferasirox effects.

Long Term Toxicity Studies

In a 26-week oral study in rats (with dietary iron supplementation) at doses of 0, 30, 80 or 180 mg/kg, mortality was observed at 180 mg/kg. Cataracts, characterized by lenticular degeneration and fragmentation, vacuole formation and/or lenticular epithelial hyperplasia were present at doses ≥ 80 mg/kg. Early lenticular changes were observed at 30 mg/kg. Cytoplasmic vacuolation of renal cortical tubular epithelium and splenic hematopoiesis occurred at 180 mg/kg. Ulceration/erosion of the glandular stomach was observed at ≥ 80 mg/kg. With the exception of the lenticular cataracts, all effects were reversible following a non-dosing phase.

Oral administration of deferasirox to marmosets for 39 weeks at doses of 0, 20, 40 or 80 mg/kg resulted in mortality at 80 mg/kg. Histopathology findings at 80 mg/kg consisted of vacuolation of the hepatic bile duct cells; vacuolation and/or degeneration of the renal cortical tubules and dilatation of medullary tubules.

Fertility

Deferasirox at oral doses up to 75 mg/kg/day (which resulted in a drug exposure (plasma AUC) that was less than the maximum human value) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Reproduction and Developmental Toxicology

Deferasirox was not teratogenic in rats or rabbits treated with doses up to and exceeding the maximum tolerated doses. Increased skeletal variations were seen in rats at a maternotoxic dose of 100 mg/kg/day, which achieved a drug exposure (plasma AUC) that was similar to the maximum human value. No adverse effect on fetal development was observed in rabbits at a maternotoxic dose of 50 mg/kg/day, which achieved a drug exposure about 30% of the maximum human value.

In a rat study designed to evaluate for effects on pre- and post-natal development, rats were treated at doses up to 90 mg/kg/day, a dose lethal to maternal animals, from early gestation to end of lactation. This treatment resulted in an increase in the number of stillborn pups and reduced pup birth weight.

Mutagenicity

Deferasirox was negative in the Ames test and an *in vitro* chromosome aberration assay with human peripheral blood lymphocytes. Positive responses were observed in an *in vitro* (V79) micronucleus screening test and in a rat *in vivo* bone marrow micronucleus assay, which may have been a result of altered hematopoiesis due to iron chelation. No response was observed in another rat *in vivo* micronucleus assay (liver) with doses up to 250 mg/kg.

Carcinogenicity

Deferasirox was not carcinogenic in a 104-week study in Wistar rats or in a 26-week study in transgenic p53+/- heterozygous mice that were maintained on an iron-supplemented diet.

In the rat carcinogenicity study, rats were administered deferasirox daily for 2 years at doses up to 60 mg/kg resulting in plasma exposure that were 28 to 39% of human exposure at 20 mg/kg based on plasma $AUC_{0\text{-}24hr}$.

In the mouse oral carcinogenicity study, transgenic p53+/- heterozygous mice were treated daily for 26 weeks at doses up to 200 mg/kg in males and 300 mg/kg in females, which resulted in plasma exposures that were 122% and 210% of human exposure at 20 mg/kg, respectively, based on plasma $AUC_{0\text{-}24hr}$.

104-week rat carcinogenicity study
No deferasirox-related neoplastic or non-neoplastic lesions were detected.

26-week transgenic mouse carcinogenicity study
No deferasirox-related neoplastic lesions were observed. Non-neoplastic lesions observed in mice were generally similar to those observed in 26 week toxicity study in rats and included biliary hyperplasia and hepatic periportal inflammation.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrJADENU® (90 mg, 180 mg, and 360 mg deferasirox tablets), submission control 260690, Product Monograph, Novartis Pharmaceuticals Canada Inc., Aug 16, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEVA-DEFERASIROX (TYPE J)

deferasirox tablets
90 mg, 180 mg, 360 mg

Read this carefully before you start taking TEVA-DEFERASIROX (TYPE J) and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TEVA-DEFERASIROX (TYPE J).

Serious Warnings and Precautions

TEVA-DEFERASIROX (TYPE J) will be prescribed to you by a healthcare professional experienced in the treatment of chronic iron overload due to blood transfusions.

TEVA-DEFERASIROX (TYPE J) has not been studied in people with severe kidney and liver problems.

Serious side effects that can happen with the use of TEVA-DEFERASIROX (TYPE J) include:
- acute kidney failure
- liver failure
- ulcer or bleeding in the stomach or intestines

See the **Serious side effects and what to do about them** table, below for information on these and other serious side effects.

This medicine is also available as a tablet that is meant to be dissolved in liquid before drinking. The doses of these two formulations are not the same. Be sure you are taking the right type of deferasirox. Talk to your healthcare professional if you are not sure.

What is TEVA-DEFERASIROX (TYPE J) used for:

TEVA-DEFERASIROX (TYPE J) is used to treat chronic iron overload in:
- adult patients and children aged 6 years and older who receive blood transfusions for the treatment of anemias;
- children aged 2 to 5 years who receive blood transfusions for the treatment of anemias, and who cannot be adequately treated with deferoxamine;
- adult patients and children aged 10 years and older with thalassemia syndromes who do not require regular blood transfusions for the treatment of anemia.

How does TEVA-DEFERASIROX (TYPE J) work?

TEVA-DEFERASIROX (TYPE J) contains the medicinal ingredient deferasirox which is an iron chelating agent. It removes the excess iron from the body (also called iron overload). This reduces the risk of organ damage caused by iron overload.

What are the ingredients in TEVA-DEFERASIROX (TYPE J)?

Medicinal ingredient: deferasirox.

Non-medicinal ingredients: core tablet: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, poloxamer, povidone; film-coating material: FD&C Blue #2/ indigo carminine aluminum lake, hypromellose, polyethylene glycol, talc, titanium dioxide.

TEVA-DEFERASIROX (TYPE J) comes in the following dosage form:

Film-coated tablets: 90 mg, 180 mg, 360 mg

Do not use TEVA-DEFERASIROX (TYPE J) if:

- you are allergic (hypersensitive) to deferasirox or any of the other ingredients of TEVA-DEFERASIROX (TYPE J) (see **What are the ingredients in TEVA-DEFERASIROX (TYPE J)?**)
- you have severe kidney disease.
- you have an advanced stage of myelodysplastic syndrome (MDS) or advanced cancer.
- you have low levels of platelets in your blood.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-DEFERASIROX (TYPE J). Talk about any health conditions or problems you may have, including if you:

- have severe heart problems (acute cardiac failure).
- have ulcers or bleeding in the stomach or intestines.
- are taking any medicines that can cause ulcers, such as:
  - non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids used to treat pain and inflammation
  - medicines used to treat osteoporosis
  - medicines used to prevent or treat blood clots
- have liver or kidney problems.
- have eye or vision problems.
- have hearing problems.
- have blood disorders (low level of platelets or white blood cells).
- have skin problems.
- are using any other iron chelation therapy to treat your iron overload.
- are 65 years of age or older. You may be more at risk of side effects.

Other warnings you should know about:

Serious Skin Reactions:

- TEVA-DEFERASIROX (TYPE J) can cause serious skin reactions, called severe cutaneous adverse reactions (SCARs), that can be fatal. These include:
  - Steven's Johnson syndrome (SJS)

- toxic epidermal necrolysis (TEN)
- hypersensitivity vasculitis
- drug reaction with eosinophilia and systemic symptoms (DRESS)
- erythema multiforme

- Symptoms can include rash, red skin, pain, swelling or blistering of the lips, eyes or mouth, skin peeling, high fever, flu-like symptoms and swollen lymph glands. If you notice any of these symptoms while you are taking TEVA-DEFERASIROX (TYPE J), tell your healthcare professional immediately.

Children and Adolescents (age 2 years to 16 years):

- Your healthcare professional will monitor your child's growth and development during treatment with TEVA-DEFERASIROX (TYPE J).
- Talk to your healthcare professional right away if your child becomes sick (vomiting, diarrhea or trouble drinking fluids) while taking TEVA-DEFERASIROX (TYPE J). Your child may be dehydrated. If this happens, TEVA-DEFERASIROX (TYPE J) treatment may need to be interrupted. Your child will be treated for dehydration to prevent kidney problems.
- Treatment with TEVA-DEFERASIROX (TYPE J) can cause liver problems including liver failure that might lead to death in children. Liver failure has also happened with kidney problems in some children. Your healthcare professional will monitor how well your child's liver and kidneys are working.

Pregnancy and Breastfeeding:

- You should not take TEVA-DEFERASIROX (TYPE J) if you are pregnant unless clearly necessary.
- If you are pregnant, or think that you may be pregnant, talk to your healthcare professional.
- TEVA-DEFERASIROX (TYPE J) may make hormonal birth control less effective. This may put you at risk of getting pregnant. While you are taking TEVA-DEFERASIROX (TYPE J) you should use another form of birth control or use an additional barrier method, such as condoms. Talk to your healthcare professional about the birth control options that are right for you.
- You should not breastfeed during treatment with TEVA-DEFERASIROX (TYPE J).

Driving and Using Machines:

- TEVA-DEFERASIROX (TYPE J) can cause dizziness. Give yourself time after taking TEVA-DEFERASIROX (TYPE J) to see how you feel before driving or operating any tools or machinery.

Blood Tests and Monitoring:

- You will have regular blood and urine tests before and during treatment with TEVA-DEFERASIROX(TYPE J). You may also be assessed by Magnetic Resonance Imaging (MRI). These tests will monitor the amount of iron in your body (level of ferritin) to see how well TEVA-DEFERASIROX (TYPE J) is working. The tests will also monitor the health of your kidneys and liver.
- Your healthcare professional will decide when to perform these tests and will interpret the results. This will help to decide on the dose of TEVA-DEFERASIROX (TYPE J) that is right for you. They will also use these tests to decide when you should stop taking TEVA-DEFERASIROX (TYPE J).
- Your eyesight and hearing will also be tested before you start taking TEVA-DEFERASIROX (TYPE J) and periodically during treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-DEFERASIROX (TYPE J):

- Antacids (medicines used to treat heartburn) containing aluminum should not be taken at the same time of day as TEVA-DEFERASIROX (TYPE J).
- cyclosporine (used to help prevent organ rejection)
- simvastatin, cholestyramine (used to lower cholesterol)
- hormonal birth control
- medicines used to treat pain and anti-inflammatory (e.g. acetylsalicylic acid, ibuprofen, corticosteroids)
- oral bisphosphonates (used to treat osteoporosis)
- anticoagulant medicines (used to prevent or treat blood clots)
- repaglinide (used to treat diabetes)
- rifampicin (used to treat tuberculosis)
- paclitaxel (used in cancer treatment)
- phenytoin, phenobarbital (used to treat epilepsy)
- ritonavir (used in the treatment of HIV infection)
- theophylline (used to treat breathing problems such as asthma)
- busulfan (used as treatment prior to bone marrow transplant)

How to take TEVA-DEFERASIROX (TYPE J):

- Always take TEVA-DEFERASIROX (TYPE J) exactly as your healthcare professional has told you. You should check with your healthcare professional if you are not sure.
- Take TEVA-DEFERASIROX (TYPE J) once a day, every day, at about the same time each day.
- TEVA-DEFERASIROX (TYPE J) should be taken on an empty stomach or with a light meal. 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 with lettuce, tomato, and 1 packet mustard).
- Swallow the tablets whole with water or other liquids.
- If you have difficulty swallowing, TEVA-DEFERASIROX (TYPE J) tablets may be crushed and the full amount of medicine sprinkled in a soft food such as yogurt or applesauce. The food with the medicine should be immediately and completely consumed. Do not store it for future use.

Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your body weight and the condition that is be treated.

The daily dose of TEVA-DEFERASIROX (TYPE J) may be adjusted or interrupted. This will depend on how you respond to the treatment and if you experience certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-DEFERASIROX (TYPE J), contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you take too much TEVA-DEFERASIROX (TYPE J) you may have abdominal pain, diarrhea, nausea or vomiting. You may also have serious liver or kidney problems.

Missed Dose:

If you miss a dose, take it as soon as you remember on that day. Take your next dose as scheduled. Do not take a double dose on the next day to make up for the forgotten dose. Do not take more than one dose on the same day.

What are possible side effects from using TEVA-DEFERASIROX (TYPE J)?

These are not all the possible side effects you may have when taking TEVA-DEFERASIROX (TYPE J). If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Gastrointestinal problems such as nausea, vomiting, diarrhea, pain in the abdomen, bloating, constipation, indigestion
- Skin rash
- Headache
- Dizziness
- Fever
- Sore throat
- Swelling of arms or legs
- Change in the colour of the skin
- Anxiety
- Sleep disorder
- Tiredness
- Hearing loss

Serious side effects what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Eye or vision problems: blurred or cloudy eyesight, partial loss of vision		√	
Hearing problems: reduced hearing, hearing loss		√	
Pancreatitis (inflammation of the pancreas): severe upper stomach pain that lasts and gets worse when you lie down, nausea, vomiting		√	

Serious side effects what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Gastrointestinal bleeding: vomiting blood, black or tarry stools		√	
Ulcer: frequent heartburn or abdominal pain particularly after eating or taking the drug		√	
Blood problems (low white and/or red blood cells or platelets): feeling tired or weak, pale skin, bruising or bleeding for longer than usual after you cut yourself, fever, chills, mouth sores, frequent infections		√	
RARE			
Acute renal failure (severe kidney problems): decreased urination, nausea, vomiting, swelling of extremities, fatigue		√	
Allergic reactions: difficulty breathing or swallowing, dizziness, rash, hives, swelling of the face, lips, tongue or throat			√
Serious skin reactions: severe rash, red or dry skin, pain, blisters and peeling skin that may start around the lips, nose, eyes, mouth and genitals and spread elsewhere, high fever, flu-like symptoms, swollen lymph glands, swelling of the face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			√
VERY RARE			
Liver problems: drowsiness, upper right abdominal pain, yellowing or increased yellowing of your skin or eyes, dark urine, pale stool, nausea, vomiting, loss of appetite		√	
UNKNOWN FREQUENCY			
Gastrointestinal perforation (a hole in the wall of your stomach or intestine): severe abdominal pain and tenderness, nausea, vomiting, chills, fever			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of the reach and sight of children and of pets.
- Do not use TEVA-DEFERASIROX (TYPE J) after the expiry date which is stated on the package/carton after EXP. The expiry date refers to the last day of that month.
- Store between 15°C-30°C.
- Store in the original package in order to protect from moisture.

If you want more information about TEVA-DEFERASIROX (TYPE J):

- Talk to your healthcare professional
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.tevacanada.com); or by contacting Teva Canada Limited by:

  Phone: 1-800-268-4127 ext. 3;
  Email: druginfo@tevacanada.com; or
  Fax: 1-416-335-4472

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