

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **Taro-Deferasirox**
deferasirox

Dispersible Tablets for Suspension, 125 mg, 250 mg, or 500 mg, Oral

Iron chelating agent

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Date of Initial Authorization:
JUN 26, 2017

Date of Revision:
JUN 21, 2023

Submission Control No: 268762

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX	06/2023
4 DOSAGE AND ADMINISTRATION; 4.2 Recommended Dose and Dosage Adjustment	06/2023
7 WARNINGS AND PRECAUTIONS	06/2023
7 WARNINGS AND PRECAUTIONS; 7.1.3 Pediatrics	06/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Taro-Deferasirox (deferiasirox) dispersible 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 Taro-Deferasirox 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 deferiasirox in children aged 2 to 5 (see [7.1.3 Pediatrics](#)). The overall exposure of deferiasirox 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 deferiasirox (see [7.1.4 Geriatrics](#)). The pharmacokinetics of deferiasirox 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

Taro-Deferasirox is contraindicated in:

- patients with estimated creatinine clearance <60 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal.
- 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 $< 50 \times 10^9/L$.
- patients with hypersensitivity to the active substance, deferiasirox, 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 Taro-Deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

Taro-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](#))

Taro-Deferasirox dispersible tablets is a formulation of deferasirox with lower bioavailability compared to deferasirox film-coated tablets. (see [4.2 Recommended Dose and Dosage Adjustment](#)). Taro-Deferasirox requires a different dosing regimen and method of administration compared to deferasirox film-coated 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 film-coated tablet that is meant to be swallowed whole. 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

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

4. 2 Recommended Dose and Dosage Adjustment

A. Transfusional iron overload:

- It is recommended that therapy with Taro-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. Taro-Deferasirox is available in three strengths (125, 250 and 500 mg).
- 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.
- Taro-Deferasirox should be taken on an empty stomach at least 30 minutes before eating the first meal of the day, preferably at the same time each day.

a. *Starting Dose*

The recommended initial daily dose of Taro-Deferasirox is 10, 20, or 30 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 10 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 20 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 20 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 30 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.

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, doses of 10, 20 and 30 mg/kg 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, doses of 10, 20 and 30 mg/kg 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)	n	Iron excretion (mg/kg/day)	Iron excretion (mg/year)		Iron excretion (transfusion unit equivalents/year)	
			20kg patient	50 kg patient	20kg Patient	50 kg patient
5	8	0.13 ± 0.10	939 ± 726	2349 ± 1816	4.7 ± 3.6	11.7 ± 9.1
10	44	0.22 ± 0.14	1572 ± 1055	3930 ± 2638	7.9 ± 5.3	19.6 ± 13.2
20	64	0.39 ± 0.15	2841 ± 1102	7102 ± 2756	14.2 ± 5.5	35.5 ± 13.8
30	108	0.60 ± 0.23	4378 ± 1712	10945 ± 4280	21.9 ± 8.6	54.7 ± 21.4

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 Taro-Deferasirox 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 5 or 10 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. Doses of Taro-Deferasirox should not exceed 30 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](#)). In patients with beta-thalassemia not adequately controlled with daily doses of 30 mg/kg, doses of up to 40 mg/kg may be considered.

As with other iron chelator treatment, the risk of toxicity of Taro-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. If the serum ferritin falls below 1000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the dose is greater than 25 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 Taro-Deferasirox in the 20-40 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 Taro-Deferasirox.

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 microgram/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. Taro-Deferasirox is available in three strengths (125, 250 and 500 mg).

Taro-Deferasirox should be taken on an empty stomach at least 30 minutes before eating the first meal of the day, preferably at the same time each day.

a. Starting Dose

The recommended initial daily dose of Taro-Deferasirox is 10 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 over-chelation (see [7 WARNINGS AND PRECAUTIONS](#)). Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 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 15mg/kg is limited. Doses above 20 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 $\leq 2,000$ microgram/L, dosing should not exceed 10 mg/kg.

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

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

Conversion from Deferasirox film-coated tablets to Taro-Deferasirox dispersible tablets: For patients who are currently on chelation therapy with Deferasirox film-coated tablets and converting to deferasirox dispersible tablets for oral suspension, the dose of deferasirox dispersible tablets for oral suspension should be about 30% higher, rounded to the nearest whole tablet. The [table](#) below provides additional information on dosing conversion to deferasirox dispersible tablets for oral suspension.

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

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

Geriatrics (≥ 65 years of age): The pharmacokinetics of deferasirox dispersible tablets 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 dispersible tablets has been associated with serious and fatal adverse reactions in pediatric patients in the post-marketing 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 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 deferasirox dispersible tablets 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 deferasirox dispersible tablets 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 Taro-Deferasirox dispersible tablets use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs.

Patients with renal impairment: deferasirox dispersible tablets 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 deferasirox dispersible tablets use. Use the minimum effective deferasirox dispersible tablets 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 deferasirox dispersible tablets to prevent severe and irreversible renal injury.

For adult patients, the daily dose of Taro-Deferasirox should be reduced by 10 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. 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 10 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, Taro-Deferasirox therapy should be interrupted (see [8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data](#)).

Patients with hepatic impairment: deferasirox dispersible tablets 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%. Taro-Deferasirox 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 deferasirox treatment should be interrupted.

Patients with skin rash: Skin rashes may occur during deferasirox treatment. Severe skin rashes may require interruption of deferasirox 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.

4.3 Reconstitution

Oral Solutions:

- Reconstitution: Taro-Deferasirox tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of < 1 g should be dispersed in 100 mL of liquid and doses of > 1 g in 200 mL of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed. Tablets must not be chewed, split, crushed or swallowed whole.
- Incompatibilities: Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

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 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 90mg/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 by 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	Dispersible tablets for oral suspension 125 mg, 250 mg, or 500 mg deferasirox	lactose monohydrate, crospovidone, povidone (K29/32), sodium lauryl sulphate, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

Taro-Deferasirox (deferasirox dispersible tablets for oral suspension) is available in three strengths: 125 mg, 250 mg and 500 mg.

- 125 mg: Off-white, round uncoated tablets, flat with beveled edge, debossed with “568” on one side and plain on other side.
- 250 mg: Off-white, round uncoated tablets, flat with beveled edge, debossed with “569” on one side and plain on other side.
- 500 mg: Off-white, round uncoated tablets, flat with beveled edge, debossed with “570” on one side and plain on other side.

Taro-Deferasirox is supplied in bottle pack with child resistant closure of 30’s and 60’s dispersible tablets and blister pack of 30 dispersible tablets.

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 Taro-Deferasirox when administered with other iron chelation therapy has not been established.

No studies on the effects of Taro-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

See [16 NON-CLINICAL TOXICOLOGY –Carcinogenicity and Genotoxicity](#) sections.

Cardiovascular

Taro-Deferasirox has not been studied in patients with acute cardiac failure due to iron overload. Therefore, the use of Taro-Deferasirox 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 Taro-Deferasirox treatment and thereafter at regular intervals.

The frequency of auditory adverse events irrespective of causality was increased among pediatric patients who received deferasirox doses greater than 25 mg/kg/day 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 Taro-Deferasirox 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 deferasirox 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 Taro-Deferasirox 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](#)).

Taro-Deferasirox contains lactose (0.85 mg lactose for each mg of deferasirox). This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

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 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 deferasirox should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with deferasirox may be considered, once the cause of the cytopenia has been elucidated.

Hepatic/Biliary/Pancreatic

Taro-Deferasirox 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, deferasirox 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 Taro-Deferasirox 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 deferasirox in the 20-40 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, Taro-Deferasirox should be discontinued and appropriate medical intervention instituted. Taro-Deferasirox 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 deferasirox in the 20-40 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 microgram/L, temporary interruption of Taro-Deferasirox therapy should be considered. 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 and monitored weekly for the first month followed by monthly thereafter. Tests for proteinuria should be performed monthly (see Renal section above).

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 Taro-Deferasirox should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with Taro-Deferasirox 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 Taro-Deferasirox 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 Taro-Deferasirox 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](#)).

Deferasirox 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 in pooled clinical trials (n=158) found a higher rate of renal adverse events among patients receiving doses greater than 25 mg/kg/day 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 Taro-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 over-chelation 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 Taro-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 Drug Reactions](#)).

Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose and during therapy. It is recommended that serum creatinine and/or creatinine clearance be assessed twice before initiating therapy. Weekly monitoring of serum creatinine and/or 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 Taro-Deferasirox 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, Taro-Deferasirox 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 deferasirox treatment. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. Upon suspicion of any SCAR, Taro-Deferasirox should be discontinued immediately and should not be reintroduced.

Skin rashes: skin rashes may also appear during Taro-Deferasirox treatment. For rashes of mild to moderate severity, Taro-Deferasirox may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Taro-Deferasirox 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 TOXICOLOGY – Reproductive and Developmental Toxicology](#)). The potential risk for humans is unknown. It is therefore recommended that Taro-Deferasirox should not be used during pregnancy. Patients taking oral contraceptives may be at risk of getting pregnant because deferasirox 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 (see [16 NON-CLINICAL TOXICOLOGY – Reproductive and Developmental Toxicology](#)). Therefore, women should be advised against breast-feeding while taking Taro-Deferasirox.

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 in pooled clinical trials (n=158) found a higher rate of renal adverse events among patients receiving doses greater than 25 mg/kg/day 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 post-marketing setting. These events were frequently associated with volume depletion or with continued deferasirox doses in the 20-40 mg/kg/day range 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 Taro-Deferasirox 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 Taro-Deferasirox use in the setting of decreased renal function. Avoid use of other nephrotoxic drug.

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; β-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 \geq 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 Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for 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 Ophthalmologic](#)).

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 Dispersible tablets for oral solution - treated Patients in Study A2209

	Deferasirox dispersible tablets	Deferasirox dispersible tablets	Placebo	Placebo	Placebo
	5 mg/kg/day	10mg/kg/day	5 mg/kg/day	10mg/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)
Diarrhoea	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 dispersible tablets for oral solution-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 Dispersible tablets 5 mg/kg (N=55) n (%)	Deferasirox Dispersible tablets 5 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 \leq 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 \geq 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 Dispersible tablets 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)
Pharyngolaryngeal pain	31 (10.5)	43 (14.8)
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 Dispersible tablets 10 mg/kg N=143	Deferasirox Dispersible tablets 20 mg/kg N=106	Deferasirox Dispersible tablets 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)
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)
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/1.73m²) and 621 matched-controls with normal kidney function (eGFR >120 ml/min/1.73 m²) 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 dosage starting at 20 mg/kg/day (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 dosage >30 mg/kg/day, 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 dose >25 mg/kg/day 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 Drug Reactions

The less common adverse events (<1%) which occurred in clinical trials and considered to be related to deferasirox dispersible tablets are listed below.

Cardiovascular: QT prolongation¹

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 pancreatitis²

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 dispersible tablets 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 dispersible tablets 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 dispersible tablets therapy.

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

Laboratory parameter	Deferasirox dispersible tablets 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 dispersible tablets 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 dispersible tablets. Rarely biopsy proven interstitial nephritis has also been reported. Acute renal failure (mostly serum creatinine increases $\geq 2x$ upper limit of normal, and usually reversible after treatment interruption), hematuria, renal tubular necrosis. Renal tubulopathy has been reported in patients treated with deferasirox dispersible tablets. 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, gastrointestinal perforation

Blood and lymphatic system disorders

Agranulocytosis, neutropenia, thrombocytopenia and aggravated anemia

Hypocalcemia has been reported to occur during deferasirox dispersible tablets therapy

Hepatic/Biliary/Pancreatic

Hepatic failure.

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 dispersible tablets and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, deferasirox dispersible tablets 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 dispersible tablets 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 deferasirox 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 dispersible tablets (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 deferasirox dispersible tablets with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox dispersible tablets efficacy. If deferasirox dispersible tablets and a potent UGT inducer are used concomitantly, increases in the dose of deferasirox dispersible tablets 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 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 dispersible tablets (repeated dose of 30 mg/kg/day) 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 deferasirox dispersible tablets and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between deferasirox dispersible tablets 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 dispersible tablets (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 deferasirox dispersible tablets and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between deferasirox dispersible tablets 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 deferasirox is combined with busulfan and the patient's plasma concentrations of busulfan should be monitored.

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

Use with Vitamin C: The concomitant administration of deferasirox dispersible 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 deferasirox dispersible tablets with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of deferasirox dispersible tablets in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see [7 WARNINGS AND PRECAUTIONS](#)).

Use with hydroxyurea: The interaction of deferasirox dispersible tablets 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

The exposure (AUC) of deferasirox was increased when taken along with food (see [10 CLINICAL PHARMACOLOGY](#)). Taro-Deferasirox should be taken on an empty stomach at least 30 minutes before eating the first meal of the day, preferably at the same time each day (see [4 DOSAGE AND ADMINISTRATION](#)).

Taro-Deferasirox tablets for oral suspension can be dispersed in water, orange juice or apple juice. Dispersion of Taro-Deferasirox in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Interactions

Interactions between deferasirox dispersible tablets 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 Taro-Deferasirox therapy be interrupted at least five days before gallium-67 scintigraphy.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Taro-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 aluminium. 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 showed that deferasirox (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 (0.1-0.5 mg Fe/kg/day). Iron excretion was predominantly fecal.

Daily treatment with deferasirox dispersible tablets 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 dispersible tablets 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.

In patients with non-transfusion-dependent thalassemia syndromes and iron overload, treatment with deferasirox 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.

Cardiac Electrophysiology: The effect of 20 and 40 mg/kg of deferasirox 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 18-65 years. No evidence of prolongation of the QTc interval was observed in this study; however, the relevance of this study to long-term deferasirox dispersible tablets use is unknown.

In patients with cardiac iron deposition (MRI T2* <20 ms), treatment with Deferasirox dispersible tablets was shown to remove cardiac iron as demonstrated by progressive improvements in T2* values over 3 years of observation. In patients without cardiac de position, Deferasirox dispersible tablets 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

Absorption

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

Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content > 50% of calories) and increased by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately elevated when taken 30 minutes before meals with normal content (25% elevation) or high fat content (13% elevation). Deferasirox dispersible tablets must therefore be taken on an empty stomach at least 30 minutes before eating, preferably at the same time each day (see [4 DOSAGE and ADMINISTRATION](#)).

The total exposure (AUC) to deferasirox when taken after dispersion of tablets in orange juice or apple juice was equivalent to the exposure after dispersion in water (relative AUC ratios of 103% and 90%, respectively).

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.

Excretion

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

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 dispersible tablets 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, STABILITY AND DISPOSAL

Store at room temperature (15-30°C). Protect from moisture.

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

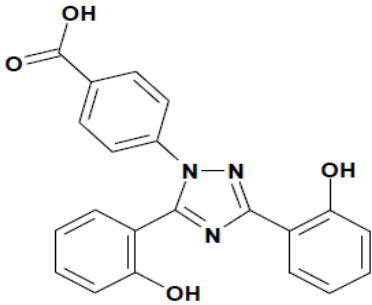
12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	deferasirox
Chemical name:	4-[3,5-bis-(2-hydroxyphenyl)-[1,2,4]-triazol-1-yl] benzoic acid
Molecular formula and molecular mass:	C ₂₁ H ₁₅ N ₃ O ₄ ; 373.37 g/mol
Structural formula:	

Physicochemical properties:	<i>Physical Form:</i> white to slightly yellow powder <i>Solubility:</i> 0.4 mg/mL at pH 7.40, 25°C
pH:	The pH of a 0.5% (m/V) suspension of deferasirox in water at 22-25°C is 4.10

14 CLINICAL TRIALS

14.1 Clinical Trial 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 dispersible 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 dispersible 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 dispersible 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 dispersible 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 dispersible 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 dispersible 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 dispersible tablets for oral suspension and deferoxamine in patients with sickle cell disease and transfusional hemosiderosis. As in Study 0107, patients received 5, 10, 20, or 30, mg/kg per day of deferasirox dispersible 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 dispersible tablets for oral suspension 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 dispersible 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 dispersible tablets by baseline LIC: 5, 10, 20, or 30 mg/kg DFO by baseline LIC [‡] : 20-30, 25-35, 35-50, >50	Deferasirox dispersible tablets =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 dispersible tablets by baseline LIC: 5, 10, 20, or 30 mg/kg Duration: 52 weeks	Deferasirox dispersible tablets =184	35.0 ± 22.4 (3-81)	93 (50.5%) / 91 (49.5%)
0109	open-label, randomized, Phase II, active comparator control study	Deferasirox dispersible tablets 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 dispersible tablets =132 DFO =63	19.2 ± 10.9 (3-54)	80 (41.0%) / 115 (59.0%)

[‡] LIC: liver iron concentration

SD: standard deviation

DFO: deferoxamine

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

Deferiasirox 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 dispersible tablets for oral suspension	DFO
Biopsy & SQUID	n=276	n=277
Success rate (n (%))	146 (52.9)	184
95% CI	[47.0, 58.8]	(66.4)
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
95% CI	[51.7, 65.6]	(58.9)
Difference [95% CI]	-0.3 [-10.2, 9.6]	

DFO: deferoxamine

The primary efficacy population consisted of 553 patients (deferasirox dispersible tablets for oral suspension 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 dispersible tablets for oral suspension 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 dispersible tablets for oral suspension doses of 20 or 30 mg/kg and deferoxamine doses of ≥ 35 mg/kg. The success rates with deferasirox dispersible tablets for oral suspension 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 dispersible 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

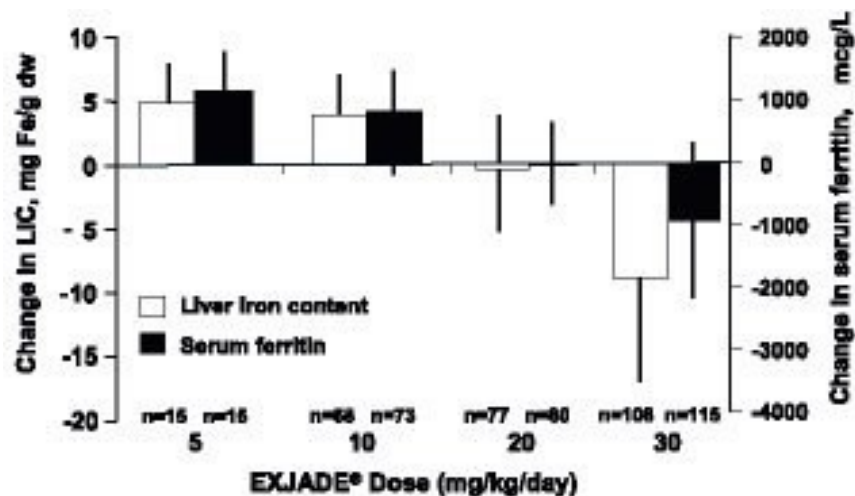
Protocol Recommended Dose (mg/kg/day)		Mean actual prescribed dose (mg/kg/day)		Ratio of iron excretion/iron intake		Serum ferritin levels (mcg/L) Mean change from baseline \pm SD	
Deferasirox tablets for oral suspension	Deferoxamine	Deferasirox tablets for oral suspension	Deferoxamine	Deferasirox tablets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

SD: standard deviation

Reduction of LIC and serum ferritin were observed with deferasirox dispersible tablets for oral suspension doses of 20 to 30 mg/kg. Deferasirox dispersible 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 is recommended (see [4 DOSAGE AND ADMINISTRATION](#)).

Figure 1 Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox dispersible tablets (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 dispersible tablets for oral suspension. 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 dispersible 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 dispersible tablets for oral suspension 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 dispersible 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 dispersible tablets for oral suspension ($n=113$) 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 $\geq 56\%$: 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 starting dose was 30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. In the prevention cohort, the deferasirox 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 \pm coefficient of variation) significantly increased from a baseline value of 11.2 ms \pm 40.5% to 12.9 ms \pm 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 \pm 5.7% to 67.1 \pm 6.0%. In the prevention cohort, myocardial T2* remained within the normal range and was unchanged from a baseline value of 32.0 ms \pm 25.6% to 32.5 ms \pm 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 dispersible tablets 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 (N=62)	62 (100.0)		4 (6.5)	16 (25.8)	40 (64.5)	2 (3.2)
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 dispersible 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 dispersible tablets for oral suspension 5 mg/kg/day or deferasirox dispersible tablets for oral suspension 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 microgram/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 dispersible tablets treatment groups compared with placebo ([Table 15](#)). Furthermore, a statistically significant dose effect of deferasirox dispersible 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 dispersible tablets for oral suspension 5 mg/kg/day (N=55)	Deferasirox dispersible 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 dispersible tablets for oral suspension - 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 dispersible tablets for oral suspension 10 mg/kg and 5 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 dispersible tablets 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 dispersible tablets 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 dispersible tablets for oral suspension group compared to the 5 mg/kg/day deferasirox dispersible tablets for oral suspension group (56.4% versus 32.7%, respectively). In addition, a reduction of $\geq 30\%$ in LIC between baseline and Week 52 was reported in approximately twice as many patients in the 10 mg/kg/day deferasirox dispersible tablets for oral suspension group (49.15%) compared to the 5 mg/kg/day deferasirox dispersible tablets for oral suspension group (25.5%). After one year of treatment, 27.3% of patients in the 10 mg/kg/day deferasirox dispersible tablets for oral suspension group and 14.5% of patients in the 5 mg/kg/day deferasirox dispersible tablets for oral suspension group achieved an LIC of < 5 mg Fe/g dw.

In the deferasirox dispersible tablets for oral suspension 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 Comparative Bioavailability Studies

A blinded, randomized two-treatment, two-period, single oral dose (1 x 500 mg), crossover comparative bioavailability study of Taro-Deferasirox dispersible tablets for suspension, 500 mg (Taro Pharmaceuticals Inc.) and EXJADE®• dispersible tablets for suspension, 500 mg (Novartis Pharmaceuticals Canada Inc.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data

Deferasirox (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (mcg.h/ml)	142.24 149.36 (32.56)	150.34 162.42 (45.36)	95.3	89.5 to 101.6
AUC _I (mcg.h/ml)	146.78 154.65 (34.16)	155.20 167.88 (45.58)	95.3	89.5 to 101.5
C _{max} (mcg/ml)	10.95 11.21 (21.36)	11.81 12.29 (30.35)	93.4	87.0 to 100.2
T _{max} ³ (h)	3.28 (25.96)	3.06 (32.85)		
T _½ ³ (h)	11.48 (22.92)	11.34 (21.97)		

¹ Taro-Deferasirox (deferasirox) dispersible tablets for suspension, 500 mg (Taro Pharmaceuticals Inc.)

² PrEXJADE® (deferasirox) dispersible tablets for suspension, 500 mg (Novartis Pharmaceuticals Canada Inc.)

³ Expressed as arithmetic mean (CV%)

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 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 \geq 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 \geq 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 \geq 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.

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_{0-24hr}.

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_{0-24hr}.

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.

Genotoxicity: 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.

Reproduction and Developmental Toxicology:

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.

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Exjade (Dispersible Tablets for Suspension, 125 mg, 250 mg and 500 mg), submission control 260689, Product Monograph, Novartis Pharmaceutical Canada Inc. AUG 16, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

P^rTaro-Deferasirox **deferasirox dispersible tablets for suspension**

Read this carefully before you start taking **Taro-Deferasirox** 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 **Taro-Deferasirox**.

Serious Warnings and Precautions

- Taro-Deferasirox will be prescribed to you by a healthcare professional experienced in the treatment of chronic iron overload due to blood transfusions.
- Taro-Deferasirox has not been studied in people with severe kidney and liver problems.
- Serious side effects that can happen with the use of Taro-Deferasirox include:
 - acute kidney failure
 - liver failure
 - ulcer or bleeding in the stomach or intestinesSee 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 film-coated tablet that is meant to be swallowed whole. 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 Taro-Deferasirox used for?

Taro-Deferasirox 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 Taro-Deferasirox work?

Taro-Deferasirox contains the medicinal ingredient deferasirox which is an iron chelating agent. It removes the excess iron from the body (also called iron overload), thereby reducing the risk of organ damage caused by iron overload.

What are the ingredients in Taro-Deferasirox?

Medicinal Ingredient: deferasirox.

Non-medicinal ingredients: Lactose monohydrate, crospovidone, povidone, sodium lauryl sulphate, microcrystalline cellulose, silicon dioxide and magnesium stearate.

Taro-Deferasirox comes in the following dosage forms:

dispersible tablets for oral suspension: 125 mg, 250 mg, 500 mg

Do not Use Taro-Deferasirox if:

- you are allergic (hypersensitive) to deferasirox or any of the other ingredients of Taro-Deferasirox (see *What are the ingredients in Taro-Deferasirox*).
- 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 Taro-Deferasirox. Talk about any health conditions or problems you may have, including if you:

- have severe heart problems (acute cardiac failure).
- have ulcer 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.
- are lactose intolerant or have one of the following rare hereditary diseases:
 - Galactose intolerance
 - Lapp lactase deficiency
 - Glucose-galactose malabsorptionbecause lactose is a non-medicinal ingredient in Taro-Deferasirox.
- have eye or vision problems.
- have hearing problems

- have blood disorders (a low level of platelets or white blood cell count)
- have skin problem.
- are using any other iron chelation therapy to treat your iron overload.
- are 65 years of age or older. You may be at risk of side effects.

Other warnings you should know about:

Serious Skin Reactions:

- Taro-Deferasirox can cause serious skin reactions, called severe cutaneous adverse reactions (SCARs), that can be fatal. These include:
 - Stevens- 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 Taro-Deferasirox 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 Taro-Deferasirox.
- Talk to your healthcare professional right away if your child becomes sick (vomiting, diarrhea or trouble drinking fluids) while taking Taro-Deferasirox. Your child may be dehydrated. If this happens, Taro-Deferasirox treatment may need to be interrupted. Your child will be treated for dehydration to prevent kidney problems.
- Treatment with Taro-Deferasirox 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 Taro-Deferasirox if you are pregnant, unless clearly necessary.
- If you are pregnant, or think that you may be pregnant, talk to your healthcare professional immediately.
- Taro-Deferasirox may make hormonal birth control less effective. This may put you at risk of getting pregnant. While you are taking Taro-Deferasirox 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 Taro-Deferasirox.

Driving and using machines:

- Taro-Deferasirox can cause dizziness. Give yourself time after taking Taro-Deferasirox to see how you feel before driving or operating any tools or machinery.

Blood Test and Monitoring:

- You will have regular blood and urine tests before and during treatment with Taro-Deferasirox. You may also be assessed by Magnetic Resonance Imaging (MRI). These will monitor the amount of iron in your body (level of ferritin) to see how well Taro-Deferasirox 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 Taro-Deferasirox that is right for you. They will also use these tests to decide when you should stop taking Taro-Deferasirox.
- Your eyesight and hearing will also be tested before you start taking Taro-Deferasirox 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 Taro-Deferasirox:

- Antacids (medicines used to treat heartburn) containing aluminum should not be taken at the same time of day as Taro-Deferasirox.
- cyclosporine (used to help prevent organ rejection)
- simvastatin, cholestyramine (used to lower cholesterol)
- hormonal birth control
- medicines used to treat pain and inflammation (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 Taro-Deferasirox:

- Always take Taro-Deferasirox exactly as your healthcare professional has told you. You should check with your healthcare professional if you are not sure.
- **Drop** the tablet(s) into a glass of water, orange or apple juice (100 mL for doses of less than 1 g, and 200 mL for doses of 1 g or more).
- **Stir** until the tablet(s) dissolve completely. The liquid in the glass will look cloudy.
- **Drink** everything in the glass. Then add a little water or juice to what is left in the glass and drink that too.



- Do not dissolve the tablets in fizzy drinks or milk.
- Do not chew, break or crush the tablets. Do not swallow the tablets whole.
- Take Taro-Deferasirox once a day, every day, at about the same time each day.
- Taro-Deferasirox must be taken on an empty stomach.
- Wait at least 30 minutes after taking Taro-Deferasirox before eating the first meal of the day.

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 to be treated.

The daily dose of Taro-Deferasirox 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 Taro-Deferasirox, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms

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 Taro-Deferasirox?

These are not all the possible side effects you may have when taking Taro-Deferasirox. 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
- Hair loss

Serious side effects and 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		✓	
Gastrointestinal bleeding: vomiting blood, black or tarry stools		✓	
Ulcer: frequent heartburn or abdominal pain particularly after eating or taking the drug		✓	

Serious side effects and 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	
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 reaction: difficulty breathing or swallowing, dizziness, rash, hives, swelling of the face, lips, tongue or throat			✓
Serious skin reactions: severe rash, red or dry itchy skin, purple or red spots on the 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 Taro-Deferasirox 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 at room temperature (15-30°C).

Store in the original package in order to protect from moisture.

If you want more information about Taro-Deferasirox:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare 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 www.taro.ca, or by calling 1-800-268-1975.

This leaflet was prepared by Taro Pharmaceuticals Inc.
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Last revised: June 21, 2023