

PREScribing INFORMATION

DEFRIJET (Deferasirox Film-coated Tablets 360 mg)

COMPOSITION

DEFRIJET

Each Film coated Tablet contains:

Deferasirox Ph. Eur360 mg

Excipients:

Cellulose, Microcrystalline, Crospovidone, Povidone, Poloxamer, Purified Water, Silica colloidal anhydrous, Magnesium Stearate (Veg), Opadry Blue 00F505015

DESCRIPTION

Dark blue colored, biconvex, oval shape, film coated tablet with beveled edges, debossed with '360' on one side and plain on other side.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC03

Mechanism of action

Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the feces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Pharmacodynamics (PD)

Deferasirox at daily doses of 10, 20 and 40 mg/kg induced the mean net excretion of 0.119, 0.329, and 0.445 mg Fe/kg body weight/day, respectively in iron overloaded adult thalassemic patients.

Deferasirox has been reported to be investigated in adult and pediatric patients (aged 2 years and older) with chronic iron overload due to blood transfusions. The underlying conditions requiring transfusion included beta-thalassemia, sickle cell disease, and other congenital and acquired anemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anemia and other very rare anemias).

Daily treatment with deferasirox at doses of 20 and 30 mg/kg for one year in frequently transfused adult and pediatric patients with beta-thalassemia has been reported to lead 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 microgram/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 reportedly 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 (see **DOSE AND METHOD OF ADMINISTRATION**). Serum ferritin assessed by monthly monitoring reflected changes in liver iron concentration indicating that trends in serum ferritin can be used to monitor response to therapy.

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

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 has been reported to lead 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 reported in patients treated with placebo. In addition, treatment with deferasirox at a dose of 10 mg/kg/day for one year reportedly led to a reduction in mean serum ferritin from baseline by -222.0 microgram/L, while an increase of 114.5 microgram/L was reported in patients treated with placebo.

Pharmacokinetics

Absorption

Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from deferasirox tablets is about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been reported. Reportedly bioavailability of deferasirox film-coated tablets was 36% greater than that with deferasirox dispersible tablets.

After a high-fat meal, AUC and C_{max} have been reported to increase (by 18% and 29%, respectively). The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that deferasirox film-coated tablets should be taken either on an empty stomach or with a light meal.

Distribution

Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 L in adults.

Biotransformation

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 inhibition of deferasirox metabolism by hydroxyurea has been reported *in vitro*. Deferasirox undergoes enterohepatic recycling. Reportedly administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

Elimination

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

Linearity / non-linearity

The C_{max} and AUC_{0-24h} of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3.

Special populations

Pediatric patients

The overall exposure of adolescents (12 to ≤ 17 years) and children (2 to < 12 years) to deferasirox after single and multiple doses was reported to be lower than that in adult patients. In children younger than 6 years old exposure has been reported to be about 50 % lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

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 is not expected to have clinical consequences.

Elderly patients

The pharmacokinetics of deferasirox has not been reported in elderly patients (aged 65 or older).

Renal or hepatic impairment

The pharmacokinetics of deferasirox has not been reported in patients with renal impairment.

The average AUC of deferasirox in subjects with mild hepatic impairment (Child-Pugh A) reportedly increased 16% over that found in subjects with normal hepatic function, while the average AUC of deferasirox in subjects with moderate hepatic impairment (Child-Pugh B) reportedly increased 76% over that found in subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment reportedly increased 22% over that found in subjects with normal hepatic function (see **DOSE AND METHOD OF ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**). The pharmacokinetics of deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

INDICATIONS

Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).

Deferasirox is also indicated for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and over.

DOSE AND METHOD OF ADMINISTRATION

Deferasirox is available at the strength of 360 mg film coated tablet only and may not be suitable for all the dosing recommendations and formulations mentioned below. In such cases, other approved strength/formulations must be used.

Transfusional iron overload

Dosage regimen

It is recommended that therapy with deferasirox be started after the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 microgram/L). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

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.

For patients who are currently on chelation therapy with deferasirox dispersible tablets and switching to deferasirox film-coated tablets, the dose of deferasirox film-coated tablets should be 30% lower than the dose of deferasirox dispersible tablets, rounded to the nearest whole tablet as shown in Table 3.

Starting dose

The recommended initial daily dose of deferasirox is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg may be considered 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 reduction of iron overload.

An initial daily dose of 7 mg/kg may be considered 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 the body iron level.

For patients already well-managed on treatment with deferoxamine, a starting dose of deferasirox that is numerically one third that of the deferoxamine dose could be considered as shown in tables 1 and 3 (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 14 mg/kg/day of deferasirox).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of deferasirox is adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 21 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 28 mg/kg may be considered. Doses above 28 mg/kg are not recommended because there is only limited reported experience with doses above this level.

In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range and to minimize the risk of overchelation (see **WARNINGS AND PRECAUTIONS**). If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see **WARNINGS AND PRECAUTIONS**).

The corresponding recommended doses for both formulations are shown in Table 1.

Table 1: Transfusional iron overload: Recommended doses

	Deferasirox Dispersible tablets	Deferasirox Film-coated tablets	Transfusions		Serum ferritin
Starting dose	20 mg/kg/day	14 mg/kg/day	After 20 units (about 100 mL/kg) of PRBC*	or	>1,000 microgram/L
Alternative starting doses	30 mg/kg/day	21 mg/kg/day	>14 mL/kg/month of PRBC* (approx. >4 units/month for an adult)		
	10 mg/kg/day	7 mg/kg/day	<7 mL/kg/month of PRBC* (approx. <2 units/month for an adult)		
For patients well managed on deferoxamine**	Half of deferoxamine dose	One third of deferoxamine dose			
Adjustment steps (every 3 to 6 months)	Increase				>2,500 microgram/L
	5 to 10 mg/kg/day Up to 40 mg/kg/day	3.5 to 7 mg/kg/day Up to 28 mg/kg/day			
	Decrease				
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
	When target is reached				500 to 1,000 microgram/L
Maximum dose	40 mg/kg/day	28 mg/kg/day			
Consider dose interruption					<500 microgram/L

* Packed Red Blood Cells

** Dose conversion explained in more detail in Table 3

Non-transfusion-dependent thalassemia (NTDT) syndromes

Dosage

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 overchelation.

For patients who are currently on chelation therapy with deferasirox dispersible tablets and switching to deferasirox film-coated tablets, the dose of deferasirox film-coated tablets should be 30% lower than the dose of deferasirox dispersible tablets, rounded to the nearest whole tablet.

Starting dose

The recommended initial daily dose of deferasirox is 7 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see **WARNINGS AND PRECAUTIONS**). Every 3 to 6 months of treatment, consider a dose increase in increments of 3.5 to 7 mg/kg if the patient's LIC is ≥ 7 mg Fe/g dw, or serum ferritin is consistently $>2,000$ microgram/L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.

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

For patients in whom the dose was increased to >7 mg/kg, dose reduction is recommended to 7 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 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is reported evidence from clinical monitoring that chronic iron overload is present.

The corresponding recommended doses for both formulations are shown in Table 2.

Table 2: NTDT: Recommended doses

	Deferasirox Dispersible tablets	Deferasirox Film-coated tablets	Liver iron concentration (LIC)*		Serum ferritin
Starting dose	10 mg/kg/day	7 mg/kg/day	≥ 5 mg Fe/g dw	or	>800 microgram/L
Adjustment steps	Increase		≥ 7 mg Fe/g dw		$>2,000$ microgram/L

(every 3 to 6 months)	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 microgram/L
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
Maximum dose	20 mg/kg/day	14 mg/kg/day			
	10 mg/kg/day	7 mg/kg/day	Not assessed	and	≤2,000 microgram/L
Dose interruption			<3 mg Fe/g dw	or	<300 microgram/L
Re-initiation			if clinical evidence of chronic iron overload		

*LIC is the preferred method of determining iron overload.

Transfusional iron overload and non-transfusion-dependent thalassemia syndromes

Information on dose conversion between DT and FCT, as well as deferoxamine is shown in Table 3 below.

Table 3: Dose conversion

Deferoxamine dose**	Daily dose of deferasirox Dispersible tablets	Daily dose for deferasirox Film-coated tablets
10 mg/kg	5 mg/kg	3.5 mg/kg
20 mg/kg	10 mg/kg	7 mg/kg
30 mg/kg	15 mg/kg	10.5 mg/kg
40 mg/kg	20 mg/kg	14 mg/kg
50 mg/kg	25 mg/kg	17.5 mg/kg
60 mg/kg	30 mg/kg	21 mg/kg
Not applicable*	35 mg/kg	24.5 mg/kg
Not applicable*	40 mg/kg	28 mg/kg

* Not recommended in deferoxamine label

**For patients already well-managed on treatment with deferoxamine

Special populations

Patients with renal impairment

Deferasirox treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 7 mg/kg (see **WARNINGS AND PRECAUTIONS**).

Patients with hepatic impairment

For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50%. Deferasirox should not be used in patients with severe hepatic impairment (Child-Pugh C) (see **WARNINGS AND PRECAUTIONS** and **PHARMACODYNAMIC AND PHARMACOKINETIC**).

PROPERTIES). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see **WARNINGS AND PRECAUTIONS**).

Pediatric patients

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 **WARNINGS AND PRECAUTIONS**). Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

Elderly patients

The dosing recommendations for elderly patients are the same as described above. Elderly patients reportedly experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

Method of administration

The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, deferasirox film-coated tablets may be crushed and administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree). The dose should be immediately and completely consumed, and not stored for future use. Deferasirox film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal.

CONTRAINDICATIONS

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

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

Hypersensitivity to deferasirox or to any of the excipients.

WARNINGS AND PRECAUTIONS

The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy (see **DOSE AND METHOD OF ADMINISTRATION**).

Caution should be used in elderly patients due to a higher frequency of adverse reactions.

Renal Impairment

Non-progressive rises in serum creatinine have been reported in patients treated with deferasirox, usually within the normal range. This has been reported in both pediatric and adult patients with iron overload during

the first year of treatment. The non-progressive nature of these serum creatinine observations has been reported.

Cases of acute renal failure have been reported following the post-marketing use of deferasirox (see **UNDESIRABLE EFFECTS**). Although causal relationship with deferasirox could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

It is recommended that serum creatinine and/or creatinine clearance should be assessed in duplicate before initiating therapy and monitored 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. Therefore, serum creatinine and/or creatinine clearance should be monitored weekly in the first month after initiation or modification of therapy (including switching formulation), and monthly thereafter. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

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 microgram/L.

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

Tests for proteinuria should be performed monthly.

Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria should be monitored as needed.

Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting.

For adult patients, the daily dose of deferasirox may be reduced by 7 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see **DOSE AND METHOD OF ADMINISTRATION**). For pediatric patients, the dose may be reduced by 7 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, deferasirox should be interrupted. Therapy with deferasirox may be reinitiated depending on the individual clinical circumstances. The recommendations for renal function monitoring are summarized in the Table 4.

Table 4: Recommendations for renal function monitoring

	Serum creatinine		Creatinine clearance
Before initiation of therapy	Twice (2x)	and/or	Twice (2x)

Contraindicated	>2 times age-appropriate ULN*	or	<40 mL/min
Monitoring	Monthly	and/or	Monthly
	For patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress the renal function as they may be more at risk of complications in the first month after initiation, or modification of therapy (including switching formulation), monitoring should be:		
	Weekly	and/or	Weekly
Reduction of daily dose by 10 mg/kg/day (deferasirox dispersible tablets), and by 7 mg/kg/day (deferasirox film-coated tablets), respectively if following renal parameters are observed on two consecutive visits and cannot be attributed to other causes:			
Adult patients	>33% above pre-treatment average (non-progressive rise)		
Pediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult patients	>33% above pre-treatment average (non-progressive rise)		
Pediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and pediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic Impairment

Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see section **DOSE AND METHOD OF ADMINISTRATION** and **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**). Deferasirox treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox was not reported to be influenced by such transaminase levels. Deferasirox is principally eliminated by glucuronidation and is minimally (about 8%) metabolized by oxidative cytochrome P450 enzymes (see **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**).

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been reported. There have been post-marketing reports of hepatic failure in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients (see **UNDESIRABLE EFFECTS**). 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 a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of deferasirox treatment at a lower dose followed by gradual dose escalation may be considered.

Blood disorders

There have been post-marketing reports (both spontaneous and from reported clinical studies) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing hematologic disorders that are frequently associated with bone marrow failure (see **UNDESIRABLE EFFECTS**). The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with deferasirox should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with deferasirox may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal disorders

Gastrointestinal irritation may occur during deferasirox treatment. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been reported in some patients (see **UNDESIRABLE EFFECTS**). Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during deferasirox therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

Caution should be exercised in patients who are taking deferasirox in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see **DRUG INTERACTIONS**), and in patients with platelet counts $<50 \times 10^9/L$.

Hypersensitivity reactions

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 **UNDESIRABLE EFFECTS**). If reactions are severe, deferasirox should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

Skin disorders

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life-threatening or fatal have been reported. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If any SCAR is suspected deferasirox should be discontinued immediately and should not be reintroduced.

Rare cases of erythema multiforme have been reported during deferasirox treatment.

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

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment (see **UNDESIRABLE EFFECTS**). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.

Other considerations

As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. 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 (see **DOSE AND METHOD OF ADMINISTRATION**).

Deferasirox has not been reported to be associated with growth retardation in children followed for up to 5 years. However, as a general precautionary measure, body weight and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

Effects on ability to drive and use machines

No studies on the effects of deferasirox on the ability to drive and use machines have been reported. Patients experiencing the uncommon adverse effect of dizziness should exercise caution when driving or operating machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The most frequent reactions reported during chronic treatment with deferasirox in adult and pediatric patients with transfusional iron overload include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea, or abdominal pain), and skin rash in about 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see **WARNINGS AND PRECAUTIONS**).

Elevations of liver transaminases were reported in about 2% of patients with transfusional iron overload. These were not dependent on dose and most of these patients had elevated levels 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%). There have been post-marketing reports of hepatic failure in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

Diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events reported by patients with non-transfusion-dependent thalassemia syndromes and iron overload receiving 10 mg/kg/day of deferasirox. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8%, respectively, of patients receiving 10 mg/kg/day of deferasirox. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal were reported in 1.8% of patients treated with 10 mg/kg/day of deferasirox.

As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly reported in patients treated with deferasirox (see **WARNINGS AND PRECAUTIONS**).

The following adverse drug reactions, listed in Table below, have been reported following treatment with deferasirox. Adverse reactions are ranked below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated summary of adverse drug reactions from reported clinical studies (Table 5)

Table 5: Adverse drug reactions reported with deferasirox

Psychiatric disorders	
Uncommon	anxiety, sleep disorder
Nervous system disorders	
Common	headache
Uncommon	dizziness
Eye disorders	
Uncommon	cataract, maculopathy
Rare	optic neuritis
Ear and labyrinth disorders	
Uncommon	deafness
Respiratory, thoracic and mediastinal disorders	
Uncommon	laryngeal pain
Gastrointestinal disorders	
Common	diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon	gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis
Rare	oesophagitis
Hepatobiliary disorders	
Common	transaminases increased
Uncommon	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	

Common	rash, pruritus
Uncommon	pigmentation disorder
Rare	erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	
Very common	blood creatinine increased
Common	proteinuria
Uncommon	renal tubular disorder (Fanconi syndrome), glycosuria
General disorders and administration site conditions	
Uncommon	pyrexia, oedema, fatigue

A comparable safety profile has been reported for film-coated and dispersible tablets.

Listing of Adverse drug reactions from post-marketing spontaneous reports

Spontaneously reported adverse reactions, presented in Table 6 below, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 6: Adverse drug reactions derived from spontaneous reports (frequency not known)

Immune system disorders	hypersensitivity reaction (including anaphylactic reaction and angioedema)
Gastrointestinal disorders	gastrointestinal perforation
Hepatobiliary disorders	hepatic failure
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
Renal and urinary disorders	renal tubular necrosis, acute renal failure (mostly serum creatinine increases $\geq 2\times$ upper limit of normal, and usually reversible after treatment interruption), tubulointerstitial nephritis

Description of selected adverse drug reactions

Cytopenias

There have been post-marketing reports (both spontaneous and from reported clinical studies) of cytopenias including neutropenia, thrombocytopenia, and aggravated anaemia in patients treated with deferasirox. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see **WARNINGS AND PRECAUTIONS**). The relationship of these episodes to treatment with deferasirox is uncertain.

Pancreatitis

Cases of serious acute pancreatitis were reported with and without documented underlying biliary conditions.

Pediatric population

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 $<1,500$ microgram/L.

No unexpected safety findings regarding adverse events (AEs) or laboratory abnormalities have been reported in children aged 2 to <6 years (at enrollment) with transfusional hemosiderosis receiving deferasirox. Increases in serum creatinine of $>33\%$ and above the upper limit of normal (ULN) on ≥ 2 consecutive occasions were

reported in 3.1% of children and elevation of alanine aminotransferase (ALT) greater than 5 times the ULN was reported in 4.3% of children. The most frequently reported AEs with reported suspected relationship to study drug were increase in ALT (21.1%), increase in aspartate aminotransferase (AST, 11.9%), vomiting (5.4%), rash (5.0%), increase in blood creatinine (3.8%), abdominal pain (3.1%) and diarrhoea (1.9%). Overall growth and development were not reported to be affected in this paediatric population.

DRUG INTERACTIONS

Agents that may decrease deferasirox systemic exposure

It has been reported that the concomitant administration of deferasirox (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% to 51%). Therefore, the concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy. If deferasirox and a potent UGT inducer are used concomitantly, increases in the dose of deferasirox should be considered based on clinical response to therapy.

Interaction with food

The C_{max} of deferasirox was reported to moderately increase by 29% when taken with a high-fat meal. Deferasirox may be taken either on an empty stomach or with a light meal.

Interaction with midazolam and other agents metabolized by CYP3A4

It has been reported that the concomitant administration of deferasirox and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% to 26%). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

Interaction with repaglinide and other agents metabolized by CYP2C8

It has been reported that the concomitant administration of deferasirox (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% (90% CI: 103% to 164%) and 62% (90% CI: 42% to 84%), respectively. When deferasirox and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolized by CYP1A2

It has been reported that the concomitant administration of deferasirox (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. Therefore, the concomitant use of deferasirox with theophylline is not

recommended. When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates may be possible.

Interaction 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.

Other Information

No interaction was reported between deferasirox and digoxin.

The concomitant administration of deferasirox and vitamin C has not been formally reported. Doses of vitamin C up to 200 mg per day have not been reported to be associated with adverse consequences.

The safety profile of deferasirox in combination with other iron chelators (deferoxamine, deferiprone) was reported to be consistent with that characterized for monotherapy.

The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally reported. Although deferasirox has a lower affinity for aluminum than for iron, deferasirox tablets must not be taken with aluminum-containing antacid preparations.

Concomitant administration of deferasirox with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see **WARNINGS AND PRECAUTIONS**).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no reported clinical data on exposed pregnancies for deferasirox. Some reproductive toxicity at maternally toxic doses have been reported in animals (see *Animal data*). The potential risk for humans is unknown.

As a precaution, it is recommended that deferasirox not be used during pregnancy unless clearly necessary.

Data

Animal data

The potential for toxicity to reproduction was reported in rats and rabbits.

Deferasirox was reported not to be teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother.

Deferasirox reportedly did not cause other effects on fertility or reproduction.

Lactation

Risk summary

It is not known if deferasirox is transferred into human milk.

Deferasirox was reported to be rapidly and extensively transferred into maternal milk in animals. No effects on the offspring were reported at maternally non-toxic doses of deferasirox. Breast-feeding while taking deferasirox is not recommended.

Females and males of reproductive potential

Contraception

Caution should be exercised when deferasirox is combined with hormonal contraceptive agents that are metabolized through CYP3A4 due to a possible decrease in efficacy of contraceptive agents (see **DRUG INTERACTIONS**).

Infertility

No effect on fertility or reproduction was reported in rats even at toxic doses of deferasirox.

OVERDOSE

Single doses up to 40 mg/kg in normal subjects have been reported to be well tolerated.

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

There is no specific antidote for deferasirox. Standard procedures for management of overdose (e.g. induction of emesis or gastric lavage) may be indicated as well as symptomatic treatment, as medically appropriate.

PRECLINICAL SAFETY DATA

No special hazard for patients with iron overload has been reported based on reported conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. The main reported findings were kidney toxicity and lens opacity (cataracts). Similar findings were reported in neonatal and juvenile animals. The kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron. See **PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**.

INCOMPATIBILITIES

Not applicable.

Pack Style:

3 aluminum blister strips containing 10 tablets each is packed in one show box. (30 tablets)

STORAGE

Do not store above 30 °C. Store in the original package in order to protect from moisture.

Shelf life

18 months

Manufactured by:

SUN Pharmaceutical Industries Ltd.
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