For the use of a Registered Medical Practitioner Only

PRESCRIBING INFORMATION
DEFRIJET 125/ 250/ 500
(Deferasirox Dispersible Tablets 125mg, 250mg, 500mg)

COMPOSITION

Each tablet contains:
Deferasirox .....…125/250/500 mg

Excipients: Lactose monohydrate, crospovidone, colloidal silicon dioxide, povidone, sodium lauryl sulphate, purified water, microcrystalline cellulose, magnesium stearate.

DESCRIPTION

DEFRIJET 125mg
Off - white, round uncoated tablets, flat with beveled edges, debossed with '568' on one side and plain on the other side

DEFRIJET 250mg
Off - white, round uncoated tablets, flat with beveled edges, debossed with '569' on one side and plain on the other side.

DEFRIJET 500mg
Off - white, round uncoated tablets, flat with beveled edges, debossed with '570' on one side and plain on the other side.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties
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 faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Pharmacodynamic effects
Mean net excretion of 0.119, 0.329 and 0.445 mg Fe/kg body weight/day, respectively has been reported with 10, 20 and 40 mg/kg daily doses of deferasirox (deferasirox tablet formulation) in iron-overloaded adult thalassaemic patients.

Pharmacokinetics

Absorption

Deferasirox (dispersible tablet formulation) is reported to be 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 (dispersible tablet formulation) is reported to be about 70% compared to an intravenous dose. Total exposure (AUC) has been reported to be approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox has been reported to be moderately (approx. 13–25%) elevated when taken 30 minutes before meals with normal or high fat content.

Distribution

Deferasirox is reported to be highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres 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: the administration of cholestyramine after a single dose of deferasirox has been reported to result in a 45% decrease in deferasirox exposure (AUC).

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*.

Elimination

Deferasirox and its metabolites are primarily excreted in the faeces (84% of the dose). Renal excretion of deferasirox and its metabolites is minimal (8% of the dose). The mean elimination half-life ($t_{1/2}$) has been reported to range from 8 to 16 hours. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

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 has been reported to increase by an accumulation factor of 1.3 to 2.3.

Characteristics in patients

Paediatric patients

The overall exposure of adolescents (12 to ≤17 years) and children (2 to <12 years) to deferasirox after single and multiple doses has been 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 have not been reported in elderly patients (aged 65 or older).

Renal or hepatic impairment
The pharmacokinetics of deferasirox have not been established in patients with renal impairment. The pharmacokinetics of deferasirox have been reported to not be influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

The average exposure of single doses of 20 mg/kg deferasirox dispersible tablets has been reported to increase by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment has been reported to increase by 22%. Exposure has been reported to increase 2.8-fold in severe hepatic impairment (Child-Pugh Class C).

INDICATIONS

DEFRIJET 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).

DEFRIJET 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

DEFRIJET is available in the strength of 125 mg, 250 mg, and 500 mg dispersible tablets only and may not be suitable for all the dosing recommendations mentioned below. In such cases, other suitable approved strengths/dosage forms of deferasirox should 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 film-coated tablets and switching to deferasirox dispersible tablets, the dose of deferasirox dispersible tablets should be 40% higher than the dose of deferasirox film-coated tablets, rounded to the nearest whole dispersible tablet.

Starting dose
The recommended initial daily dose of deferasirox is 20 mg/kg body weight.

An initial daily dose of 30 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 10 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 half 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 20 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 5 to 10 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 30 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 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 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range and to minimize the risk of overchelation (see section **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.

The corresponding recommended doses are shown in Table 1.

Table 1: Transfusional iron overload: Recommended doses

	Deferasirox Dispersible tablets	**Transfusions**		**Serum ferritin**
Starting dose	20 mg/kg/day	After 20 units (about 100 mL/kg) of PRBC*	or	>1,000 microgram/L
Alternative starting doses	30 mg/kg/day	>14 mL/kg/month of PRBC* (approx. >4 units/month for an adult)		
	10 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			
Adjustment steps (every 3 to 6 months)	Increase			>2,500 microgram/L
	5 to 10 mg/kg/day Up to 40 mg/kg/day			
	Decrease			
	5 to 10 mg/kg/day			
	When target is reached			500 to 1,000 microgram/L
Maximum dose	40 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 film-coated tablets and switching to deferasirox dispersible tablets, the dose of deferasirox dispersible tablets should be 40% higher than the dose of deferasirox film-coated tablets, rounded to the nearest whole dispersible tablet.

Starting dose

The recommended initial daily dose of deferasirox is 10 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 section **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 microgram/L and not showing a downward trend, and the patient is tolerating the drug well. 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 ≤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 ≤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 are shown in Table 2.

Table 2: NTDT: Recommended doses

	Deferasirox Dispersible tablets	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	10 mg/kg/day	≥5 mg Fe/g dw	or	>800 microgram/L
Adjustment steps (every 3 to 6 months)	Increase	≥7 mg Fe/g dw		>2,000 microgram/L
	5 to 10 mg/kg/day			
	Decrease	<7 mg Fe/g dw	or	≤2,000 microgram/L
	5 to 10 mg/kg/day			
Maximum dose	20 mg/kg/day			
	10 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 dispersible tablets and film-coated tablets, as well as deferoxamine is shown in Table 3 below.

Table 3: Dose conversion

Deferoxamine dose**	**Daily dose of deferasirox Dispersible tablets**
10 mg/kg	5 mg/kg
20 mg/kg	10 mg/kg
30 mg/kg	15 mg/kg
40 mg/kg	20 mg/kg
50 mg/kg	25 mg/kg
60 mg/kg	30 mg/kg
Not applicable*	35 mg/kg
Not applicable*	40 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 10 mg/kg (see section **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 sections **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**, **Pharmacokinetics** and **WARNINGS AND PRECAUTIONS**). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see section **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 section **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. Higher frequency of adverse reactions have been reported in elderly patients than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

Method of administration

DEFRIJET must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. The dispersible tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

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 the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Renal function

The use of deferasirox has been reported only in patients with baseline serum creatinine within the age-appropriate normal range.

Increases in serum creatinine of on ≥2 consecutive occasions, is >33%, sometimes above the upper limit of the normal range, have been reported in about 36% of patients. These have been reported to be dose-dependent. About two-thirds of the patients showing serum creatinine increase have been reported to return below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not reportedly always respond to a dose reduction or a dose interruption. In some cases, only a stabilisation of the serum creatinine values has been reported after dose reduction. Cases of acute renal failure have been reported following post-marketing use of deferasirox. In some post-marketing cases, renal function deterioration has reportedly led to renal failure requiring temporary or permanent dialysis.

The causes of the rises in serum creatinine have not been reported. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function, and in patients who are receiving high doses of deferasirox and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult). While no increase in renal adverse events has been reported after dose escalation of deferasirox dispersible tablets to doses above 30 mg/kg, an increased risk of renal adverse events with defarasirox dispersible tablet doses above 30 mg/kg cannot be excluded.

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. Serum creatinine, creatinine clearance (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels should be monitored prior to therapy, weekly in the first month after initiation or modification of therapy with deferasirox (including switch of formulation), and monthly thereafter. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting.

There have been post-marketing reports of metabolic acidosis occurring during treatment with deferasirox. The majority of these patients reportedly had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of deferasirox therapy should be considered in patients who develop metabolic acidosis.

Table 4: Dose adjustment and interruption of treatment for renal monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			**<60 ml/min**
Monitoring			
- First month after start of therapy or dose modification (including switch of formulation)	Weekly	and	Weekly
- Thereafter	Monthly	and	Monthly

Reduction of daily dose by 10 mg/kg/day (dispersible tablet formulation), if following renal parameters are observed at two consecutive visits and cannot be attributed to other causes

Adult patients	>33% above pre-treatment average	and	Decreases <LLN* (<90 ml/min)
Paediatric patients	> age appropriate ULN**	and/or	Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range **ULN: upper limit of the normal range			

Treatment may be reinitiated depending on the individual clinical circumstances.

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

- Proteinuria (test should be performed prior to therapy and monthly thereafter)
- Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox.

Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:

- Serum creatinine remains significantly elevated and
- Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi Syndrome).

Hepatic function

Liver function test elevations have been reported in patients treated with deferasirox. Post-marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant comorbidities including pre-existing liver cirrhosis. However, the role of deferasirox as a contributing or aggravating factor cannot be excluded.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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 treatment at a lower dose followed by gradual dose escalation may be considered.

Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Table 5: Summary of safety monitoring recommendations

Test	**Frequency**
Serum creatinine	In duplicate prior to therapy. Weekly during first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Proteinuria	Prior to therapy. Monthly thereafter.
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.

Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual development	Prior to therapy. Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of deferasirox might be limited and may be inferior to risks. As a consequence, treatment with deferasirox is not recommended in these patients.

Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).

The reported data in children with non-transfusion-dependent thalassaemia are very limited. As a consequence, deferasirox therapy should be closely monitored to detect adverse reactions and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with deferasirox, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal disorders

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Multiple ulcers have been reported in some patients. There have been reports of ulcers complicated with digestive perforation. Also, there have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during deferasirox therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. Caution should be exercised in patients who are taking deferasirox in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm^3 (50 x 10^9/l).

Skin disorders

Skin rashes may appear during deferasirox treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration. 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. If any SCAR is suspected, Deferasirox should be discontinued immediately and should not be reintroduced. At the

time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored.

Hypersensitivity reactions
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. If such reactions occur, deferasirox should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock.

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

Blood disorders
There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with deferasirox. Most of these patients reportedly had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations
Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy. If serum ferritin falls consistently below 500 µg/l (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), an interruption of treatment should be considered.

The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends.

Growth and sexual development of paediatric patients treated with deferasirox for up to 5 years have been reported to be unaffected. However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored prior to therapy and at regular intervals (every 12 months).

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with deferasirox.

Effects on ability to drive and use machines

Deferasirox has minor influence on the ability to drive and use machines. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machines.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23mg) per dispersible tablet that is to say essentially 'sodium free'.

USE IN SPECIAL POPULATIONS

Pregnancy
The potential risk for humans is unknown.

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

Deferasirox may decrease the efficacy of hormonal contraceptives. Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using deferasirox.

Breast-feeding
Deferasirox has been reported to be rapidly and extensively secreted into maternal milk. No effect on the offspring has been reported. It is not known if deferasirox is secreted into human milk. Breast-feeding while taking deferasirox is not recommended.

Fertility
There are no reported data on fertility in humans. No adverse effects on male or female fertility have been reported.

DRUG INTERACTIONS

The safety of deferasirox in combination with other iron chelators has not been reported. Therefore, it must not be combined with other iron chelator therapies.

Interaction with food
The bioavailability of deferasirox has been reported to increase to a variable extent when taken along with food. Deferasirox dispersible tablets must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day.

Agents that may decrease deferasirox systemic exposure

Deferasirox metabolism depends on UGT enzymes. The concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) has been reported to result in a decrease of deferasirox exposure by 44%. Therefore, the concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of deferasirox adjusted if necessary.

Cholestyramine has been reported to significantly reduce the deferasirox exposure in the degree of enterohepatic recycling.

Interaction with midazolam and other agents metabolised by CYP3A4
The concomitant administration of deferasirox dispersible tablets and midazolam (a CYP3A4 probe substrate) has been reported to result in a decrease of midazolam exposure by 17%. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents, bepridil, ergotamine).

Interaction with repaglinide and other agents metabolised by CYP2C8
The concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily, dispersible tablet formulation), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, has been reported to increase repaglinide AUC and C_{max} about 2.3-fold and 1.6-fold, respectively. Since the interaction has not been reported with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed. An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolised by CYP1A2
The concomitant administration of deferasirox as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP1A2 substrate theophylline (single dose of 120 mg) has been reported to resulted in an increase of theophylline AUC by 84%. The single dose C_{max} has not been reported to be 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. If deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

Other information
Deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox tablets with aluminium-containing antacid preparations.

The concomitant administration of deferasirox with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity. The concomitant administration of deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

UNDESIRABLE EFFECTS

Summary of the safety profile

The most frequent reactions reported during chronic treatment with deferasirox dispersible tablets in adult and paediatric patients include gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash. Diarrhea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly. These reported reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

Dose-dependent increases in serum creatinine have been reported in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been reported in both paediatric and adult patients with beta-thalassemia and iron overload during the first year of treatment, but there is evidence that this does not decrease further in subsequent years of treatment. Elevations of liver transaminases have been reported. Safety monitoring schedules for renal and liver parameters are recommended. Auditory (decreased hearing) and ocular (lens opacities) disturbances are uncommon, and yearly examinations are also recommended.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of deferasirox.

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common; common; uncommon; rare; very rare; not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse drug reactions

Blood and lymphatic system disorders	
Not known	Pancytopenia[1], thrombocytopenia[1], anaemia aggravated[1], neutropenia[1]
Immune system disorders	
Not known	Hypersensitivity reactions (including anaphylactic reactions and angioedema)[1]
Metabolism and nutrition disorders	
Not known	Metabolic acidosis[1]
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
Rare	Oesophagitis
Not known	Gastrointestinal perforation[1], acute pancreatitis[1]
Hepatobiliary disorders	
Common	Transaminases increased
Uncommon	Hepatitis, cholelithiasis
Not known	Hepatic failure[1, 2]
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Pigmentation disorder
Rare	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Not known	Stevens-Johnson syndrome[1], hypersensitivity vasculitis[1], urticaria[1], erythema multiforme[1], alopecia[1], toxic epidermal necrolysis (TEN)[1]
Renal and urinary disorders	
Very common	Blood creatinine increased
Common	Proteinuria
Uncommon	Renal tubular disorder[2] (acquired Fanconi syndrome), glycosuria
Not known	Acute renal failure[1, 2], tubulointerstitial nephritis[1], nephrolithiasis[1], renal tubular necrosis[1]
General disorders and administration site conditions	
Uncommon	Pyrexia, oedema, fatigue

1 Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

2 Severe forms associated with changes in consciousness in the context of hyperammonaemic encephalopathy have been reported.

Description of selected adverse reactions

Gallstones and related biliary disorders have been reported in about 2% of patients. Elevations of liver transaminases have been reported as an adverse reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been reported to be uncommon (0.3%). During post-marketing experience, hepatic failure, sometimes fatal, has been reported with the deferasirox dispersible tablet formulation, especially in patients with pre-existing liver cirrhosis. There have been post-marketing reports of metabolic acidosis. The majority of these patients reportedly had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Cases of serious acute pancreatitis have been reported without documented underlying biliary conditions. As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly reported in patients treated with deferasirox.

Creatinine clearance in transfusional iron overload

Mean creatinine clearance decrease of 13.2% and 9.9% has been reported during the first year of treatment with deferasirox dispersible tablets in adult and paediatric beta-thalassaemia patients respectivelyNo further decrease in mean creatinine clearance levels has been reported in patients during follow up for up to five years.

Reported data in patients with non-transfusion-dependent thalassaemia syndromes

Diarrhoea, rash, and nausea have been reported to be the most frequent drug-related adverse events in non-transfusion-dependent thalassaemia syndromes and iron overload patients treated with deferasirox dispersible tablets at a dose of 10 mg/kg/day. Abnormal serum creatinine and creatinine clearance values have been reported in 5.5% and 1.8% of patients, respectively. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal have been reported in 1.8% of patients.

Paediatric population

The growth and sexual development of paediatric patients treated with deferasirox for up to 5 years have been reported to not get affected.

Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients.

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox. In post-marketing reports, a high proportion of cases of metabolic acidosis have been reported in children in the context of Fanconi syndrome.

Acute pancreatitis has been reported, particularly in children and adolescents.

OVERDOSE

Early signs of acute overdose are digestive effects such as abdominal pain, diarrhoea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and

creatinine increased with recovery after treatment discontinuation. Fanconi syndrome has been reported with an erroneously administered single dose of 90 mg/kg which resolved after treatment.

There is no specific antidote for deferasirox. Standard procedures for management of overdose may be indicated as well as symptomatic treatment, as medically appropriate.

PRECLINICAL SAFETY DATA N/A.
Pack Style:

DEFRIJET is available as triplex blister pack of 10 tablets. Such 3 blisters are packed in Show box/carton along with Pack Insert.

STORAGE
Store below 30°C. Store in the original package in order to protect from moisture.

Manufactured by:
Sun Pharmaceutical Industries Limited
Survey No. 1012, Dadra
Union Territory Of Dadra & Nagar Haveli and Daman and Diu
IN-396193, India

Product Registration Holder:
RANBAXY (MALAYSIA) SDN. BHD.
(A SUN PHARMA company)
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Date of Revision:
January 2025

References

1. Prescribing information of JEDOXRED (Deferasirox 125, 250 and 500 dispersible tablet), Dr. Reddy's Laboratories Malaysia Sdn. Bhd., Malaysia, February 2020.
2. Summary of Product Characteristics of EXJADE 500 mg dispersible tablets (Deferasirox 500 mg), Novartis Pharmaceuticals UK Ltd., February 2022.

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