Prescribing information
JEDOXRED
Deferasirox 125, 250 and 500 dispersible tablet

COMPOSITION

Deferasirox Dispersible Tablets 500mg

Each dispersible tablet contains 500mg of Deferasirox

Cellulose Microcrystalline 193.20mg, Crospovidone 40.00mg, Sodium Lauryl Sulphate 6.20mg, PoviudoneK30 30.00mg, Microcrystalline Cellulose(pH 200) 28.00mg, Lactose monohydrate 67.00mg, Crospovidone 90.00mg, Croscarmellose sodium 30.00mg, Colloidal silicon dioxide 5.20mg ,Magnesium stearate 10.40mg and purified water q.s

Deferasirox Dispersible Tablets 250mg

Each dispersible tablet contains 250mg of Deferasirox

Cellulose Microcrystalline 48.30mg, Crospovidone 10.00mg, Sodium Lauryl Sulphate 1.55mg, PoviudoneK30 7.500mg, Microcrystalline Cellulose(pH 200) 7.00mg, Lactose monohydrate 16.75mg, Crospovidone 22.50mg, Croscarmellose sodium 7.50mg, Colloidal silicon dioxide 1.30mg ,Magnesium stearate 2.60mg and purified water Q.s

Deferasirox Dispersible Tablets 125mg

Each dispersible tablet contains 125 mg of Deferasirox

Cellulose Microcrystalline 48.30 mg, Crospovidone 10.00mg, Sodium Lauryl Sulphate 1.55 mg, PoviudoneK30 7.50 mg, Microcrystalline Cellulose(pH 200) 7.00mg, Lactose monohydrate 16.75 mg, Crospovidone 22.50mg, Croscarmellose sodium 7.50 mg, colloidal silicon dioxide 1.30 mg , Magnesium stearate 2.60 mg and purified water Q.s

CLINICAL INFORMATION

Therapeutic 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 nontransfusion-dependent thalassemia syndromes aged 10 years and over.

Posology and method of administration

Transfusional iron overload

Dosage regimen

It is recommended that therapy with Jedoxred 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 Jedoxred dispersible tablets, the dose of Jedoxred 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 Jedoxred 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 Jedoxred 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 Jedoxred).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of Jedoxred 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 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 Jedoxred 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 section WARNINGS AND PRECAUTIONS).

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

Table 1 Transfusional iron overload: Recommended doses

	Jedoxred Dispersible Tablet	**Transfusions**		**Serum ferritin**
Starting dose	20 mg/kg/day	After 20 units (about 100 mL/kg) of PRBC*	Or	>1,000 microg ram/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 microg ram/L
	5-10 mg/kg/day Up to 40 mg/kg/day			
	Decrease			
	5-10 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 Jedoxred dispersible tablets, the dose of Jedoxred 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 Jedoxred 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 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

	Jedoxred Dispersible Tablet	**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 5 to 10 mg/kg/day	≥7 mg Fe/g dw	or	>2,000 microgram/L
	Decrease 5 to 10 mg/kg/day	<7 mg Fe/g dw	or	≤2,000 microgram/L
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	<300microgram/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 Jedoxred 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
Jedoxred 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%. Jedoxred should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section WARNINGS AND PRECAUTIONS and section CLINICAL PHARMACOLOGY). 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. 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.

Method of administration

Deferasirox dispersible tablets 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 orange or apple 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. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively. The tablets must not be chewed or swallowed whole.

Contraindication

-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 the active substance or to any of the excipients

Special warnings and precautions for use

Renal function

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 occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. In some cases, only a stabilisation of the serum creatinine values has been observed 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 led to renal failure requiring temporary or permanent dialysis.

The causes of the rises in serum creatinine have not been elucidated. 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 was observed after dose escalation of deferasirox dispersible tablets to doses above 30 mg/kg,. an increased risk of renal adverse events with deferasirox 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 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).

<u>Hepatic function</u>
Liver function test elevations have been observed 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 morbidities 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).
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 observed 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 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 were not affected. 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.

Interaction with other medicinal products and other forms of interaction
The safety of deferasirox in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies.

Interaction with food
The bioavailability of deferasirox was increased 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) resulted 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 significantly reduced 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) resulted 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, increased repaglinide AUC and C_{max} about 2.3-fold and 1.6-fold, respectively. Since the interaction has not been established 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) resulted in an increase of theophylline AUC by 84%. 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. 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.

Fertility, pregnancy and lactation:
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 was found to be rapidly and extensively secreted into maternal milk. No effect on the offspring was noted. It is not known if deferasirox is secreted into human milk. Breast-feeding while taking deferasirox is not recommended.

Fertility
No fertility data is available for humans. In animals, no adverse effects on male or female fertility were found.

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.

Undesirable effects
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 reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.
Dose-dependent increases in serum creatinine occurred in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance 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 events

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]
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 (acquired Fanconi syndrome), glycosuria
Not known:	Acute renal failure[1], 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.

Description of selected adverse reactions

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were 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, were 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 had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Cases of serious acute pancreatitis were observed without documented underlying biliary conditions. As with other iron chelator treatment, high-frequency

hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.

Creatinine clearance in transfusional iron overload
A mean creatinine clearance decrease of 13.2% in adult beta-thalassaemia patients and 9.9% in paediatric beta-thalassaemia patients was observed during the first year of treatment. No further decrease in mean creatinine clearance levels was observed in patients during follow up for up to five years

Patients with non-transfusion-dependent thalassaemia syndromes
In patients with non-transfusion-dependent thalassaemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day), diarrhoea, rash, and nausea were the most frequent drug-related adverse events. Abnormal serum creatinine and creatinine clearance values were 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 were reported in 1.8% of patients.

Paediatric population
The growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not 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 occurred 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. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.
There is no specific antidote for deferasirox. Standard procedures for management of overdose may be indicated as well as symptomatic treatment, as medically appropriate.

Pharmacological 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
In iron-overloaded adult thalassaemic patients, deferasirox at daily doses of 10, 20 and 40 mg/kg (dispersible tablet formulation) induced the mean net excretion of 0.119, 0.329 and 0.445 mg Fe/kg body weight/day, respectively.

Pharmacokinetic properties

Absorption
Deferasirox (dispersible tablet formulation) 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 (dispersible tablet formulation) is about 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 by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approx. 13–25%) elevated when taken 30 minutes before meals with normal or high fat content.

Distribution
Deferasirox is 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 resulted 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 was observed *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 ($t_{1/2}$) ranged 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 increased 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 was lower than that in adult patients. In children younger than 6 years old exposure was 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 established 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 were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.
Using single doses of 20 mg/kg deferasirox dispersible tablets, the average exposure was increased by 16% in mild hepatic impairment (Child-Pugh Class A) and by 76% in moderate hepatic impairment (Child-Pugh Class B) compared to normal hepatic function. The average C_{max} of deferasirox in mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in severe hepatic impairment (Child-Pugh Class C).

PHARMACEUTICAL INFORMATION

Product Description
Jedoxred 500
White to off-white, round, flat, uncoated size 16mm tablets, with debossing ‘D’ on one side and ‘500’ on other side

Jedoxred 250
White to off-white, round, flat, uncoated size 12mm tablets, with debossing ‘D’ on one side and ‘250’ on other side

Jedoxred 125
White to off-white, round, flat, uncoated size 10mm tablets, with debossing ‘D’ on one side and ‘125’ on other side

Shelf Life
36 Months

Storage conditions
Store below 30°C

Precautions for Storage
Keep out of reach of children

Nature and contents of container
Blister Pack
Each Blister contains 7 tablets.
1 x 7’s Blister, 4 x 7’s Blister and 12 x 7’s Blister are placed in a carton containing a pack insert.

Manufactured in India by:
MSN Laboratories Private Limited
Formulation Division, Unit-II,
Sy.No. 1277 & 1319 to1324,
Nandigama (Village & Mandal)
Rangareddy District-509216,
Telangana, India.

PRODUCT REGISTRATION HOLDER
Dr. Reddy's Laboratories Malaysia Sdn. Bhd. UNIT NO. SO-29-07 AND SO-29-08, MENARA 1, STRATA OFFICE, NO. 3, JALAN BANGSAR, KL ECO CITY, 59200 KUALA LUMPUR MALAYSIA

Date of revision: January 2025