SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Deferasirox 125 mg tablets for oral suspension
Defetor 125

Deferasirox 250 mg tablets for oral suspension
Defetor 250

Deferasirox 500 mg tablets for oral suspension
Defetor 500

2. Qualitative and quantitative composition

Defetor 125
Each tablet contains 125 mg of deferasirox.
Excipient with known effect
Each tablet also contains 76.95 mg of lactose monohydrate. See section 4-4.

Defetor 250
Each tablet contains 250 mg of deferasirox.
Excipient with known effect
Each tablet also contains 153.9 mg of lactose monohydrate. See section 4-4.

Defetor 500
Each tablet contains 500 mg of deferasirox.
Excipient with known effect
Each tablet also contains 307.8 mg of lactose monohydrate. See section 4-4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Defetor 125
White to off-white coloured, flat, round, uncoated tablets with bevelled edges, debossed with "491" on one side and plain on the other side.

Defetor 250
White to off-white coloured, flat, round, uncoated tablets with bevelled edges, debossed with '490' on one side and plain on the other side.

Defetor 500
White to off-white coloured, flat, round, uncoated tablets with bevelled edges, debossed with '489' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:
- In pediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- In adult and pediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
- In adult and pediatric patients with other anaemia aged 2 years and older.

Deferasirox is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

4.2 Posology and method of administration
Treatment with deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload.

Posology

Transfusional iron overload
It is recommended that treatment be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells (PRBC) or when there is evidence from clinical monitoring that chronic iron overload is present (e.g., serum ferritin >1,000 µg/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.

In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40% higher than the dose of film-coated tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 1. Recommended doses for transfusional iron overload:

	Film-coated Tablets	**Dispersible Tablets**	**Transfusions**		**Serum Ferritin**
Starting dose	14mg/kg/day	20 mg/kg/day	After 20 units (about 100 ml/ kg) of PRBC	or	1,000 µg/l

Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/ month of PRBC (approx. >4 units/month for an adult)		
	7 mg/kg/day	10 mg/kg/day			
For patients well managed on deferoxamine	One-third of deferoxamine dose	Half of deferoxamine dose			
Monitoring					Monthly
Target range					500-1,000 µg/l
Adjustment steps (every 3-6 months)	Increase				
	3.5 - 7 mg/kg/ day	5 - 10 mg/kg/ day			<2,500 µg/l
	Up to 28 mg/ kg/day	Up to 40 mg/ kg/day			
	Decrease				
	3.5 - 7 mg/kg/ day In patients treated with doses >21 mg/ kg/day	5 - 10 mg/kg/ day In patients treated with doses >30 mg/ kg/day			<2,500 µg/l
	When the target is reached				500-1,000 µg/l
Maximum dose	28 mg/kg/day	40 mg/kg/day			
Consider interruption					

Starting dose
The recommended initial daily dose of Defetor is 20 mg/kg body weight. An initial daily dose of 30 mg/kg may be considered for patients who require a reduction of elevated body iron levels and who are also receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult).

An initial daily dose of 10 mg/kg may be considered for patients who do not require a reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained. For patients already well managed on treatment with deferoxamine, a starting dose of deferasirox dispersible tablets that is numerically half that of the deferoxamine dose could be considered (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 dispersible tablets). When this results in a daily dose of less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.

Dose adjustment
It is recommended that serum ferritin be monitored every month and that the dose of deferasirox be 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 2,500 µg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. The availability of long-term efficacy and safety data with deferasirox dispersible tablets used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 30 mg/kg, a further increase (to a maximum of 40 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 30 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 30 mg/kg, dose reductions in steps of 5 to 10 mg/kg should be considered when control has been achieved (e.g., serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

Non-transfusion-dependent thalassaemia syndromes
Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available.

Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients. In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40 % higher than the dose of film-coated tablets, rounded to the nearest whole tablet. tablet.

The corresponding doses for both formulations are shown in the table below.

Table 2. Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated Tablets	**Dispersible Tablets**	**Liver Iron concentrations (LIC)***		**Serum Ferritin**
Starting dose	7 mg/kg/day	10 mg/kg/day	≥ 5 mg Fe/g dw	or	> 800 µg/l
Monitoring					Monthly
Adjustment steps (every 3-6 months)	Increase		≥ 7 mg Fe/g dw	or	<2,000 µg/l
	3.5 - 7 mg/kg/ day	5 - 10 mg/kg/ day			
	Decrease		≥ 7 mg Fe/g dw	or	<2,000 µg/l
	3.5 - 7 mg/kg/ day	5 - 10 mg/kg/ day			
Maximum dose	14 mg/kg/day	20 mg/kg/day			
	7 mg/kg/day	10 mg/kg/day			
	For adults		Not assessed	and	<2,000 µg/l
	For paediatric patients				
Interruption			< 3 mg Fe/g dw		< 500 µg/l
Retreatment			Not recommended		

* LIC is the preferred method of iron overload determination.

Starting dose
The recommended initial daily dose of deferasirox in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment
It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product 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 thalassaemia syndromes. In patients in whom LIC was not assessed and serum ferritin is ≤2,000 µg/l, dosing should not exceed 10 mg/kg.

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

Treatment cessation
Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/l), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.

Special populations

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above. In clinical studies, elderly patients experienced a higher frequency of adverse reactions than younger patients (in particular, diarrhoea) and should be monitored closely for adverse reactions that may require a dose adjustment.

Pediatric population

Transfusional iron overload
The dosing recommendations for pediatric patients aged 2 to 17 years with transfusional iron overload are the same as for adult patients. Changes in the weight of pediatric patients over time must be taken into account when calculating the dose. In children with transfusional iron overload aged between 2 and 5 years, exposure is lower than in adults. This age group may therefore require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, followed by individual titration.

Non-transfusion-dependent thalassaemia syndromes
In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤800 µg/l.

Children from birth to 23 months
The safety and efficacy of deferasirox in children from birth to 23 months of age have not been established. No data are available.

Patients with renal impairment
Deferasirox has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min.

Patients with hepatic impairment
Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by a progressive increase up to a limit of 50 % and deferasirox must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.
Combination with other iron chelator therapies as the safety of such combinations has not been established. Patients with estimated creatinine clearance <60 ml/min.

4.4 Special warnings and precautions for use

Renal function

Deferasirox has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

During clinical studies, increases in serum creatinine of >33 % on ≥2 consecutive occasions, 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 rise in serum creatinine have not been elucidated. Particular attention should therefore be paid to the 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 in clinical studies, 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 before 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 diarrhoea 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) diarrhoea, or conditions where acid-base imbalance is a known complication. The acid-base balance should be monitored as clinically indicated in these populations.

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 4. Summary of safety monitoring recommendations

Test	**Frequency**
Serum creatinine	In duplicate before therapy. Weekly during the first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Before therapy. Weekly during the first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Proteinuria	Before 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 and aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during the 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 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 the iron burden in the paediatric population. In addition, before heavily treating 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/mm3 (50 x 109/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. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported post-marketing. The risk of other more severe skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If SJS or any other severe skin reaction is suspected, deferasirox should be discontinued immediately and should not be reintroduced.

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 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. In two clinical studies, the 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.

Excipients
Defetor contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take medicine.

4.5 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. Defetor 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. In a healthy volunteer study, 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 % (90 % CI: 37 % - 51 %). 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 a mechanistic study to determine the degree of enterohepatic recycling.

Interaction with midazolam and other agents metabolised by CYP3A4
In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablets and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17 % (90% CI: 8 % - 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 metabolised through CYP3A4 (e.g., ciclosporin, simvastatin, hormonal contraceptive agents, bepridil, ergotamine).

Interaction with repaglinide and other agents metabolised by CYP2C8
In a healthy volunteer study, 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 Cmax about 2.3-fold (90 % CI [2.03-2.63]) and 1.6-fold (90 % CI [1.42-1.84]), 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
In a healthy volunteer study, 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 % (90 % CI: 73 % to 95 %). The single dose Cmax was not affected, but an increase of theophylline Cmax 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 to theophylline.

Other information
The concomitant administration of deferasirox and aluminium-containing antacid preparations has not been formally studied. Although 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. 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
In animal studies, 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.

4.7 Effects on the ability to drive and use machines
Deferasirox has a 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.

4.8 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. Diarrhoea 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. During clinical studies, dose-dependent increases in serum creatinine occurred in about 36 % of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been observed 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.

Tabulated list of adverse reactions
Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5. List of adverse reactions

Blood and lymphatic system disorders	
Not known:	Pancytopenia1, thrombocytopenia1, anaemia aggravated1, neutropenia1
Immune system disorders	
Not known	Metabolic acidosis
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, acute pancreatitis
Hepatobiliary disorders	
Common	Transaminases increased
Uncommon	Hepatitis, cholelithiasis
Not known	Hepatic failure
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Pigmentation disorder
Not known	Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN)
Renal and urinary disorders	
Very Common	Blood creatinine increased
Common	Proteinuria
Uncommon	Renal tubular disorder (acquired Fanconi syndrome), glycosuria
Not known	Acute renal failure, tubulointerstitial nephritis, nephrolithiasis, renal tubular necrosis
General disorders and administration site conditions	
Uncommon	Pyrexia, oedema, fatigue

Adverse reactions were 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) 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 treatments, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.

Creatinine clearance in transfusional iron overload
In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload treated with deferasirox dispersible tablets in two randomised and four open-label studies of up to five years duration, a mean creatinine clearance decrease of 13.2 % in adult patients (95 % CI: -14.4 % to -12.1 %; n=935) and 9.9 % (95 % CI: -11.1 %

to – 8.6 %; n=1,142) in paediatric patients was observed during the first year of treatment. In 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed.

Clinical study in patients with non-transfusion-dependent thalassaemia syndrome
In a 1-year study in patients with non-transfusion-dependent thalassaemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day), diarrhoea (9.1 %), rash (9.1 %), and nausea (7.3 %) were the most frequent study 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
In two clinical studies, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on Google Play or Apple App Store.

4.9 Overdose
Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg of the deferasirox dispersible tablet formulation in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea. Acute signs of overdose may include nausea, vomiting, headache and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 10.7 Other medicines affecting the blood.

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 the excretion of iron, primarily in the faeces. Deferasirox has a low affinity for zinc and copper and does not cause constant low serum levels of these metals.

Pharmacodynamic effects
In an iron-balance metabolic study 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.

Clinical efficacy and safety
Clinical efficacy studies were conducted with deferasirox dispersible tablets.

Deferasirox has been investigated in 411 adults (age ≥16 years) and 292 paediatric patients (aged 2 to <16 years) with chronic iron overload due to blood transfusions. Of the paediatric patients 52 were aged 2 to 5 years. The underlying conditions requiring transfusion included beta-thalassaemia, sickle cell disease and other congenital and acquired anaemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anaemia and other very rare anaemias). Daily treatment with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/l on average, respectively. At these same doses, the ratios of iron excretion: and iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. Deferasirox induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg (dispersible tablet formulation) for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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. Limited clinical data (29 patients with normal cardiac function at baseline) using MRI indicate that treatment with deferasirox 10-30 mg/kg/ day (dispersible tablet formulation) for 1 year may also reduce levels of iron in the heart (on average, MRI T2* increased from 18.3 to 23.0.

The principal analysis of the pivotal comparative study in 586 patients suffering from beta thalassaemia and transfusional iron overload did not demonstrate the non-inferiority of deferasirox dispersible tablets to deferoxamine in the analysis of the total patient population. It appeared from a posthoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with deferasirox dispersible tablets (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron concentration <7 mg Fe/g dw treated with deferasirox dispersible tablets (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established due to imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol-specified dose. Fifty-six patients under the age of 6 years participated in this pivotal study, 28 of them receiving deferasirox dispersible tablets.
It appeared from preclinical and clinical studies that deferasirox dispersible tablets could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e., a dose of deferasirox dispersible tablets that is numerically half of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical studies.
In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, deferasirox dispersible tablets up to 20 and 30 mg/kg produced a decrease in liver iron concentration and serum ferritin comparable to that obtained in patients with beta thalassaemia.

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) with transfusional haemosiderosis received deferasirox, there were no clinically meaningful differences in the safety and tolerability profile of deferasirox in paediatric patients aged 2 to <6 years compared to the overall adult and older paediatric population, including increases in serum creatinine of >33 % and above the upper limit of normal on ≥ 2 consecutive occasions (3.1 %), and elevation of alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (4.3 %). Single events of increase in ALT and aspartate aminotransferase were reported in 20.0 % and 8.3 %, respectively, of the 145 patients who completed the study.
In a study to assess the safety of deferasirox film-coated and dispersible tablets, 173 adult and paediatric patients with transfusion-dependent thalassaemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed.

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with deferasirox dispersible tablets was assessed in a 1-year, randomised double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox dispersible tablet regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of a matching placebo (56 patients). The study enrolled 145 adult and 21 paediatric patients. The primary efficacy parameter was the change in liver iron concentration (LIC) from baseline after 12 months of treatment. One of the secondary efficacy parameters was the change in serum ferritin between baseline and fourth quarter. At a starting dose of 10 mg/kg/day, deferasirox dispersible tablets led to reductions in indicators of total body iron. On average, the liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p<0.001$). On average, serum ferritin decreased by 222.0 µg/l in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 115 µg/l in patients treated with placebo ($p<0.001$).
The European Medicines Agency has deferred the obligation to submit the results of studies with deferasirox in one or more subsets of the paediatric population in the treatment of chronic iron overload requiring chelation therapy.

5.2 Pharmacokinetic properties

Absorption
Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (tmax) 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 in a healthy volunteer study, 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 (t1/2) ranged from 8 to 16 hours. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

Linearity/non-linearity
The Cmax and AUC0-24h of deferasirox increases approximately linearly with dose understeady-statee 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 studied in elderly patients (aged 65 or older).

Renal or hepatic impairment
The pharmacokinetics of deferasirox have not been studied 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. In a clinical study using single doses of 20 mg/kg deferasirox dispersible tablets, the average exposure was increased 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 Cmax of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22 %. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C).

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. The main

findings were kidney toxicity and lens opacity (cataracts). Similar findings were observed in neonatal and juvenile animals. Kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron.

Tests of genotoxicity in vitro were negative (Ames test and chromosomal aberration test) while deferasirox caused the formation of micronuclei *in vivo* in the bone marrow, but not the liver, of noniron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

The potential for toxicity to reproduction was assessed in rats and rabbits. Deferasirox was not teratogenic but caused an increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother. Deferasirox did not cause other effects on fertility or reproduction.

6. Pharmaceutical particulars

6.1 List of excipients
Hypromellose
Microcrystalline cellulose PH 200
Lactose monohydrate
Sodium lauryl sulphate
Povidone
Colloidal anhydrous silica
Magnesium stearate
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C. Store in original package to protect from moisture.

6.5 Nature and contents of the container
The capsules are packed in aluminium cold forming blister packs.

Blister pack sizes of 3 x 10 tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
Torrent Pharmaceuticals Limited
Torrent House, Off. Ashram Road
Ahmedabad - 380 009, Gujarat
India

8. MANUFACTURER

Torrent Pharmaceuticals Limited
Indrad 382721, Kadi, Indrad
Mehsana, Gujarat state
India

9. REGISTRATION DETAILS

Defetor 125
Zimbabwe registration number: 2023/10.7/6427
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Defetor 250
Zimbabwe registration number: 2023/10.7/6426
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Defetor 500
Zimbabwe registration number: 2023/10.7/6425
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF TEXT

August 2023