SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Deferasirox 360 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 360 mg deferasirox

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off white, film-coated, oval bi-convex tablets, debossed with '58' on one side and "V" 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 paediatric 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 paediatric 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 paediatric patients with other anaemias 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 and non-transfusion-dependent thalassaemia syndromes require different posologies. All physicians who intend to prescribe Deferasirox must ensure they have received and are familiar with the physician educational material (Guide for healthcare professionals which also includes a prescriber checklist).

Transfusional iron overload

Doses (in mg/kg body weight) must be calculated and rounded to the nearest whole tablet size.

Caution should be taken during chelation therapy to minimise the risk of overchelation in all patients (see section 4.4).

In the EU, medicines containing deferasirox are available as film-coated tablets and dispersible tablets marketed under different tradenames as generic alternatives to Deferasirox. Due to different pharmacokinetic profiles, a 30% lower dose of Deferasirox film-coated tablets is needed in comparison to the recommended dose for deferasirox dispersible tablets (see section 5.1).

Starting dose

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) (see Table 1).

Table 1 Recommended starting doses for transfusional iron overload

Recommended starting dose			
Serum ferritin		**Patient population**	**Recommended starting dose**
>1 000 µg/l	or	Patients who have already received approximately 20 units (about 100 ml/kg) of PRBC.	**14 mg/kg/day**
Alternative starting doses			
Patient population			**Alternative starting dose**
Patients who do not require reduction of body iron levels and who are also receiving <7 ml/kg/month of PRBC (approx. <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.			7 mg/kg/day
Patients who require reduction of elevated body iron levels and who are also receiving >14 ml/kg/month of PRBC (approx. >4 units/month for an adult).			21 mg/kg/day
Patients who are well managed on deferoxamine.			One third of

	deferoxamine dose*
*A starting dose that is numerically one third that of the deferoxamine dose (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week [or equivalent] could be transferred to a starting daily dose of 14 mg/kg/day of Deferasirox film-coated tablets). When this results in a daily dose of <14 mg/kg, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).	

Dose adjustment
It is recommended that serum ferritin be monitored every month and that the dose of Deferasirox film-coated tablets be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin(see Table 2). Dose adjustments may be made in steps of 3.5 to 7 mg/kg/day and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden).

Table 2 Recommended dose adjustments for transfusional iron overload

Serum ferritin (monthly monitoring)	**Recommended dose adjustment**
Persistently >2 500 μg/l and not showing a decreasing trend over time	Increase dose every 3 to 6 months in steps of 3.5 to 7 mg/kg/day. **The maximum allowed dose is 28 mg/kg/day.** If only very poor haemosiderosis control is achieved at doses up to 21 mg/kg/day, a further increase (to a maximum of 28 mg/kg/day) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 21 mg/kg/day, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible.
>1 000 μg/l but persistently ≤2 500 μg/l with a decreasing trend over time	Decrease dose every 3 to 6 months in steps of 3.5 to 7 mg/kg/day in patients treated with doses >21 mg/kg/day, until the target of 500 to 1 000 μg/l is reached.
500 to 1 000 μg/l (target range)	Decrease dose in steps of 3.5 to 7 mg/kg/day every 3 to 6 months to maintain serum ferritin levels within the target range and to minimise the risk of overchelation.
Consistently <500 μg/l	Consider interruption of treatment (see section 4.4).

The availability of long-term efficacy and safety data from clinical studies conducted with deferasirox dispersible tablets used at doses above 30 mg/kg (equivalent to 21 mg/kg when given as film-coated tablets) is currently limited (264 patients followed for an average of 1 year after dose escalation).

Doses above 28 mg/kg/day are not recommended because there is only limited experience with doses above this level (see section 5.1).

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 overchelation in all patients (see section 4.4).

In the EU, medicines containing deferasirox are available as film-coated tablets and dispersible tablets marketed under different tradenames as generic alternatives to deferasirox. Due to different pharmacokinetic profiles, a 30% lower dose of Deferasirox film-coated tablets is needed in comparison to the recommended dose for deferasirox dispersible tablets (see section 5.1).

Starting dose
The recommended initial daily dose of Deferasirox film-coated tablets in patients with non-transfusion-dependent thalassaemia syndromes is 7 mg/kg body weight/day.

Dose adjustment
It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimise the risk of overchelation (see section 4.4). Recommended dose adjustments for non-transfusion-dependent thalassaemia syndromes are summarised in Table 3.

Table 3 Recommended dose adjustments for non-transfusion-dependent thalassaemia syndromes

Serum ferritin (monthly monitoring)		**Liver iron concentration (LIC)***	**Recommended dose adjustment**
Consistently >2 000 µg/l and not showing a downward trend	or	≥7 mg Fe/g dw	Increase dose every 3 to 6 months in steps of 3.5 to 7 mg/kg/day if the patient is tolerating the medicinal product well. **The maximum allowed dose is 14 mg/kg/day for adult patients and 7 mg/kg/day for paediatric patients.** Doses above 14 mg/kg/day are not recommended because there is no experience with doses above this level in patients with non-transfusion dependent thalassaemia syndromes.
≤2 000 µg/l	or	<7 mg Fe/g dw	Decrease dose every 3 to 6 months in steps of 3.5 to 7 mg/kg/day down to a dose of 7 mg/kg/day (or

			less) in patients treated with doses >7 mg/kg/day.
<300 µg/l	or	<3 mg Fe/g dw	Treatment should be stopped once a satisfactory body iron level has been achieved.
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.			
*LIC is the preferred method of iron overload determination.			

In both paediatric and adult patients in whom LIC was not assessed and serum ferritin is ≤2 000 µg/l, dosing of Deferasirox film-coated tablets should not exceed 7 mg/kg/day.

<u>*Special populations*</u>

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.

Paediatric population
Transfusional iron overload:
The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional iron overload are the same as for adult patients (see section 4.2). It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimise the risk of overchelation (see section 4.4). Changes in weight of paediatric 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 (see section 5.2). 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 of Deferacerox film-coated tablets should not exceed 7 mg/kg/day. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation (see section 4.4). 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 (see sections 4.3 and 4.4).

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 progressive increase up to a limit of 50% of recommended treatment dose for patients with normal hepatic function (see sections 4.4 and 5.2), 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 (see section 4.4).

Method of administration
For oral use.

The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

The film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination with other iron chelator therapies as the safety of such combinations has not been established (see section 4.5).

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 (see section 4.8). 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 in clinical studies, an increased risk of renal adverse events with film-coated tablet doses above 21 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 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) or diarrhoea, 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.

Post-marketing cases of severe forms of renal tubulopathy (such as Fanconi syndrome) and renal failure associated with changes in consciousness in the context of hyperammonaemic encephalopathy have been reported in patients treated with deferasirox, mainly in children. It is recommended that hyperammonaemic encephalopathy be considered and ammonia levels measured in patients who develop unexplained changes in mental status while on deferasirox therapy.

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) ▯ Thereafter	 Weekly Monthly	 and and	 Weekly Monthly
Reduction of daily dose by 7 mg/kg/day (film-coated tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			
Adult patients Paediatric patients	>33% above pre-treatment average > age appropriate ULN**	and and/or	Decreases <LLN* (<90 ml/min) Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment	and/or	Decreases <LLN* (<90 ml/min)

	average		
*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 observed in patients treated with deferasirox. Post-marketing cases of hepatic failure, some of which were fatal, have been reported. Severe forms associated with changes in consciousness in the context of hyperammonaemic encephalopathy, may occur in patients treated with deferasirox, particularly in children. It is recommended that hyperammonaemic encephalopathy be considered and ammonia levels measured in patients who develop unexplained changes in mental status while on deferasirox therapy. Care should be taken to maintain adequate hydration in patients who experience volume-depleting events (such as diarrhoea or vomiting), particularly in children with acute illness. Most reports of hepatic failure involved patients with significant comorbidities including pre-existing chronic liver conditions (including cirrhosis and hepatitis C) and multi-organ failure. The role of deferasirox as a contributing or aggravating factor cannot be excluded (see section 4.8).

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) (see section 5.2).

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 (see section 5.1). 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 (see section 4.8). 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. In case of gastrointestinal ulceration or haemorrhage, deferasirox should be discontinued and additional evaluation and treatment must be promptly initiated. 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) (see section 4.5).

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 lifethreatening 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 (see section 4.8). 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 (see section 4.3).

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported (see section 4.8). 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 and to avoid overchelation (see section 4.2). Dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels are recommended during periods of treatments with high doses and when serum ferritin levels are close to the target range. 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, growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected (see section 4.8). 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.

Deferasirox contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 (see section 4.3).

Interaction with food
The C_{max} of deferasirox film-coated tablets was increased (by 29%) when taken with a high-fat meal. Deferasirox film-coated tablets may be taken either on an empty stomach or with a light meal, preferably at the same time each day (see sections 4.2 and 5.2).

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 (see section 5.2).

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 C_{max} 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 (see section 4.4). 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 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
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 (see section 4.4). 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.

Concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC), but the mechanism of the interaction remains unclear. If possible, evaluation of the pharmacokinetics (AUC, clearance) of a busulfan test dose should be performed to allow dose adjustment.

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 (see section 5.3). 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 (see section 4.5). 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 (see section 5.3).

4.7 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent reactions reported during chronic treatment in clinical studies conducted 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 (see section 4.4).

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 (see section 4.4).

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 6

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], alopecia1, 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 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 deferasirox (see section 4.4). 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 (see section 4.4). 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 (see section 4.4).

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 syndromes
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, growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected (see section 4.4).

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 United Kingdom Yellow Card Scheme at: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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
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 (referred to below as ‘deferasirox’). Compared to the deferasirox dispersible tablet formulation, the dose of the deferasirox film-coated tablets is 30% lower than the dose of the deferasirox dispersible tablets, rounded to the nearest whole tablet (see section 5.2).

Deferasirox has been investigated in 411 adult (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 [MDS], 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: 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 milliseconds).

The principal analysis of the pivotal comparative study in 586 patients suffering from beta-thalassaemia and transfusional iron overload did not demonstrate non-inferiority of deferasirox dispersible tablets to deferoxamine in the analysis of the total patient population. It appeared from a post-hoc 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). For deferasirox film-coated tablets, a dose ratio of 3:1 can be considered (i.e. a dose of deferasirox film-coated tablets that is numerically one third 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.

A placebo-controlled randomised study was performed in 225 patients with MDS (Low/Int-1 risk) and transfusional iron overload. The results of this study suggest that there is a positive impact of deferasirox on event-free survival (EFS, a composite endpoint including non-fatal cardiac or liver events) and serum ferritin levels. The safety profile was consistent with previous studies in adult MDS patients.

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.

An open-label 1:1 randomised study was performed in 224 paediatric patients aged 2 to <18 years old with transfusion-dependant anaemia and iron overload to evaluate treatment compliance, efficacy and safety of the deferasirox granule formulation

compared to the dispersible tablet formulation. The majority of patients (142, 63.4%) in the study had beta-thalassemia major, 108 (48.2%) patients were naïve to iron chelation therapy (ICT) (median age 2 years, 92.6% aged 2 to <10 years) and 116 (51.8%) were ICT pre-treated (median age 7.5 years, 71.6% aged 2 to <10 years) of whom 68.1% had previously received deferasirox. In the primary analysis performed in ICT-naïve patients after 24 weeks of treatment, the compliance rate was 84.26% and 86.84% in the deferasirox dispersible tablets arm and in the deferasirox granules arm, respectively, with no statistically significant difference. Similarly, there was no statistically significant difference in mean changes from baseline in serum ferritin (SF) values between the two treatment arms (-171.52 μg/l [95% CI: -517.40, 174.36] for dispersible tablets [DT] and 4.84 μg/l [95% CI: -333.58, 343.27] for the granule formulation, difference between means [granules – DT] 176.36 μg/l [95% CI: -129.00, 481.72], two sided p-value = 0.25). The study concluded that treatment compliance and efficacy were no different between deferasirox granules and deferasirox dispersible tablet arms at different time points (24 and 48 weeks). The safety profile was overall comparable between the granules and the dispersible tablet formulations.

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 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, 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 ($p<0.001$).

5.2 Pharmacokinetic properties

Deferasirox film-coated tablets demonstrate higher bioavailability compared to the deferasirox dispersible tablet formulation. After adjustment of the strength, the film-coated tablet formulation (360 mg strength) was equivalent to deferasirox dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase.

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.

The absolute bioavailability of the film-coated tablet formulation has not been determined.

Bioavailability of deferasirox film-coated tablets was 36% greater than that with dispersible tablets.

A food-effect study involving administration of the film-coated tablets to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased (by 18% and 29%, respectively). The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that the film-coated tablets should be taken either on an empty stomach or with a light meal.

Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 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 ($t_{1/2}$) 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 $AUC0\text{-}_{24h}$ 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 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 C_{max} 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) (see sections 4.2 and 4.4).

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. The 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, chromosomal aberration test) while deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-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 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

Tablet core:
Cellulose, microcrystalline
Crospovidone (Type A)
Poloxamer 188
Povidone (k-30)
Silica, colloidal anhydrous
Sodium stearyl fumarate

Coating:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC/PVdC- Alu
30s blister pack.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amarox Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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