Irosix Deferasirox

1. NAME OF THE MEDICINAL PRODUCT
Irosix 90mg Film Coated Tablets
Irosix 180mg Film Coated Tablets
Irosix 360mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Irosix 90mg Film Coated Tablets: Each tablet contains 90mg of Deferasirox.
Irosix 180mg Film Coated Tablets: Each tablet contains 180mg of Deferasirox.
Irosix 360mg Film Coated Tablets: Each tablet contains 360mg of Deferasirox.
For the full list of excipients, see section List of excipients.

3. PHARMACEUTICAL FORM
Film Coated Tablets.
Irosix 90mg: Light blue color, oval, biconvex film coated tablet with bevelled edges, debossed with "N55" on one side and plain on other side.
Irosix 180mg: Medium blue color, oval, biconvex film coated tablet with bevelled edges, debossed with "N54" on one side and plain on other side.
Irosix 360mg: Dark blue color, oval, biconvex film coated tablet with bevelled edges, debossed with "N53" on one side and plain on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Irosix Film Coated Tablets are indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).
Irosix Film Coated Tablets are also indicated for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and over.

4.2 Posology and method of administration
Transfusional iron overload
Dosage regimen
It is recommended that therapy with Irosix Film Coated Tablets be started after the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 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. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.
Irosix Film Coated Tablets are a strength-adjusted formulation of Deferasirox with higher bioavailability compared to the Deferasirox dispersible tablets formulation. For patients who are currently on chelation therapy with Deferasirox dispersible tablets and switching to Irosix Film Coated Tablets, the dose of Irosix Film Coated Tablets should be 30% lower than the dose of Deferasirox dispersible tablets, rounded to the nearest whole tablet as shown in Table 3.
Starting dose
The recommended initial daily dose of Irosix Film Coated Tablets is 14 mg/kg body weight.
An initial daily dose of 21 mg/kg may be considered for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately >4 units/month for an adult), and for whom the objective is reduction of iron overload.
An initial daily dose of 7 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult), and for whom the objective is maintenance of the body iron level. For patients already well-managed on treatment with deferoxamine, a starting dose of Irosix Film Coated Tablets that is numerically one third of the deferoxamine dose could be considered as shown in tables 1 and 3 (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 14 mg/kg/day of Irosix Film Coated Tablets).
Dose adjustment
It is recommended that serum ferritin be monitored every month and that the dose of Irosix Film Coated Tablets is adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 21 mg/kg (e.g., serum ferritin levels persistently above 2500 µg/L and not showing a decreasing trend over time), doses of up to 28 mg/kg may be considered. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.
In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/L), dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range and to minimize the risk of overchelation (see section Special warnings and precautions for use). If serum ferritin falls consistently below 500 µg/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Irosix may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section Special warnings and precautions for use).

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

Table 1 Transfusional iron overload: Recommended doses

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

*Packed Red Blood Cells
** Dose conversion explained in more detail in Table 3

Non-transfusion-dependent thalassemia (NTDT) syndromes
Dosage
Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) or serum ferritin consistently >800 µg/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of overchelation.
Irosix Film Coated Tablets are strength-adjusted formulation of Deferasirox with higher bioavailability compared to the Deferasirox dispersible tablets formulation. For patients who are currently on chelation therapy with Deferasirox dispersible tablets and switching to Irosix Film Coated Tablets, the dose of Irosix Film Coated Tablets should be 30% lower than the dose of Deferasirox dispersible tablets, rounded to the nearest whole tablet.
Starting dose
The recommended initial daily dose of Irosix Film Coated Tablets is 7 mg/kg body weight.
Dose adjustment
It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see section Special warnings and precautions for use). Every 3 to 6 months of treatment, consider a dose increase in increments of 3.5 to 7 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 µg/L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.
In patients in whom LIC was not assessed and serum ferritin is ≤2,000 µg/L, dosing should not exceed 7 mg/kg.
For patients in whom the dose was increased to >7 mg/kg, dose reduction is recommended to 7 mg/kg or less when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 µg/L.
Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.
The corresponding recommended doses for both formulations are shown in Table 2.

Table 2 NTDT: Recommended doses

	Deferasirox Dispersible tablets	Irosix Film Coated Tablets	Liver iron concentration (LIC)*		Serum ferritin
Starting dose	10 mg/kg/day	7 mg/kg/day	≥5 mg Fe/g dw	or	>800 µg /L
Adjustment steps (every 3 to 6 months)	Increase		≥7 mg Fe/g dw	or	>2,000 µg /L
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
	Decrease		<7 mg Fe/g dw		≤2,000 µg /L
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
Maximum dose	20 mg/kg/day	14 mg/kg/day			
	10 mg/kg/day	7 mg/kg/day			
	For adults		Not assessed	and	≤2,000 µg /L
	For pediatric patients				
Dose Interruption			<3 mg Fe/g dw	or	<300 µg /L
Re-initiation			if clinical evidence of chronic iron overload		

*LIC is the preferred method of determining iron overload

Transfusional iron overload and non-transfusion-dependent thalassemia syndromes
Information on dose conversion between DT and FCT as well as deferoxamine is shown in Table 3 below:

Table 3 Dose conversion

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

* Not recommended in deferoxamine label
**For patients already well-managed on treatment with deferoxamine

Special populations
Patients with renal impairment
Irosix Film Coated Tablets treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 7 mg/kg (see section Special warnings and precautions for use).
Patients with hepatic impairment
For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50%. Irosix Film Coated Tablets should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section Special warnings and precautions for use). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see section Special warnings and precautions for use).
Pediatric patients
The dosing recommendations for pediatric patients are the same as for adult patients. It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see section Special warnings and precautions for use). Changes in weight of pediatric patients over time must be taken into account when calculating the dose.
Elderly patients
The dosing recommendations for elderly patients are the same as described above. Elderly patients experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

Method of administration
For oral administration.
The film coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, Irosix Film Coated Tablets may be crushed and administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree). The dose should be immediately and completely consumed, and not stored for future use. Irosix 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.

4.3 Contraindications
Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal.
High-risk myelodysplastic syndrome (MDS) patients and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy (see section Posology and method of administration).
Caution should be used in elderly patients due to a higher frequency of adverse reactions.
Renal Impairment
Non-progressive rises in serum creatinine have been noted in patients treated with Deferasirox, usually within the normal range. This has been observed in both pediatric and adult patients with iron overload during the first year of treatment. Cases of acute renal failure have been reported following the post-marketing use of Deferasirox (see section Undesirable effects). Although causal relationship with Irosix could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.
It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy and monitored monthly thereafter.
Patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function may be more at risk of complications. Therefore, serum creatinine and/or creatinine clearance should be monitored weekly in the first month after initiation or modification of therapy (including switching formulation), and monthly thereafter. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.
Renal tubulopathy has been reported in patients treated with Deferasirox. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 µg/L.
Dose reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated.
Tests for proteinuria should be performed monthly.
Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting.
For adult patients, the daily dose of Irosix Film Coated Tablets may be reduced by 7 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section Posology and method of administration). For pediatric patients, the dose may be reduced by 7 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.
If there is a progressive increase in serum creatinine beyond the upper limit of normal, Irosix Film Coated Tablets should be interrupted. Therapy with Irosix Film Coated Tablets may be reinitiated depending on the individual clinical circumstances.
The recommendations for renal function monitoring are summarized in the table 4.

Table 4 Recommendations for renal function monitoring

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

Hepatic Impairment
Irosix is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see section Posology and method of administration). Deferasirox treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of Deferasirox was not influenced by such transaminase levels. Deferasirox is principally eliminated by glucuronidation and is minimally (about 8%) metabolized by oxidative cytochrome P450 enzymes.
There have been post-marketing reports of hepatic failure in patients treated with Deferasirox. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients (see section Undesirable effects). It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, Irosix Film Coated Tablets 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 Irosix Film Coated Tablets treatment at a lower dose followed by gradual dose escalation may be considered.

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

Gastrointestinal Disorders
Gastrointestinal irritation may occur during Irosix Film Coated Tablets treatment. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Deferasirox. There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients (see section Undesirable effects). Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Deferasirox therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).
Caution should be exercised in patients who are taking Irosix Film Coated Tablets in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see section Interaction with other medicinal products and other forms of interaction), and in patients with platelet counts <50 x 10^9/L.

Hypersensitivity reactions
Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section Undesirable effects). If reactions are severe, Irosix Film Coated Tablets should be discontinued and appropriate medical intervention instituted. Irosix Film Coated Tablets should not be reintroduced in patients who have experienced previous hypersensitivity reactions on Deferasirox due to the risk of anaphylactic shock.

Skin disorders
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life-threatening or fatal have been reported. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If any SCAR is suspected Irosix Film Coated Tablets should be discontinued immediately and should not be reintroduced.
Rare cases of erythema multiforme have been reported during Irosix Film Coated Tablets treatment.
Skin rashes may appear during Irosix Film Coated Tablets treatment. For rashes of mild to moderate severity, Irosix Film Coated Tablets may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Irosix Film Coated Tablets may be re-introduced after resolution of the rash, at a lower dose followed by gradual dose escalation.

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

Other considerations
As with other iron chelator treatment, the risk of toxicity of Deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. Closer monitoring of serum ferritin levels, as well as renal and hepatic function is recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. Dose reduction may be considered to avoid overchelation (see section Posology and method of administration).
As a general precautionary measure, body weight and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

4.5 Interaction with other medicinal products and other forms of interaction
Agents that may decrease Deferasirox systemic exposure
The concomitant use of Irosix Film Coated Tablets with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Irosix Film Coated Tablets efficacy. If Irosix Film Coated Tablets and a potent UGT inducer are used concomitantly, increases in the dose of Irosix Film Coated Tablets should be considered based on clinical response to therapy.

Interaction with food
The C_{max} of Deferasirox film coated tablets was moderately increased (by 29%) when taken with a high-fat meal. Irosix Film Coated Tablets may be taken either on an empty stomach or with a light meal.
Interaction with midazolam and other agents metabolized by CYP3A4
Caution should be exercised when Deferasirox is combined with substances metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

Interaction with repaglinide and other agents metabolized by CYP2C8
When Deferasirox and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between Deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolized by CYP1A2
When Deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between Deferasirox and other CYP1A2 substrates may be possible.

Interaction with busulfan
Concomitant administration of Deferasirox and busulfan resulted in an increase of busulfan exposure (AUC). The AUC increase ranged approximately 40 to 150%. The mechanism of the interaction remains unclear. Caution should be exercised when Deferasirox is combined with busulfan and the patient's plasma concentrations of busulfan should be monitored.

Other Information
No interaction was observed between Deferasirox and digoxin in healthy volunteers.
The concomitant administration of Deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences.
The safety profile of Deferasirox in combination with other iron chelators (deferoxamine, deferiprone was consistent with that characterized for monotherapy.
The concomitant administration of Deferasirox and aluminum-containing antacid preparations has not been formally studied. Although Deferasirox has a lower affinity for aluminum than for iron, Deferasirox must not be taken with aluminum-containing antacid preparations.
Concomitant administration of Deferasirox with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of Deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see section Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation
Pregnancy
The potential risk for humans is unknown. As a precaution, it is recommended that Irosix Film Coated Tablets not be used during pregnancy unless clearly necessary.
Lactation
It is not known if Deferasirox is transferred into human milk. Breast-feeding while taking Irosix Film Coated Tablets is not recommended.
Females and males of reproductive potential
Contraception
Caution should be exercised when Deferasirox is combined with hormonal contraceptive agents that are metabolized through CYP3A4 due to a possible decrease in efficacy of contraceptive agents (see section Interaction with other medicinal products and other forms of interaction).
Infertility
No fertility data is available for humans.

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

4.8 Undesirable effects
Summary of the safety profile
In patients with transfusional iron overload, the most frequent reactions reported during chronic treatment with the Deferasirox dispersible tablet formulation in adult and pediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea, or abdominal pain), and skin rash in about 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see section Special warnings and precautions for use).
For Deferasirox dispersible tablet formulation in patients with transfusional iron overload, elevations of liver transaminases were reported in about 2% of patients. These were not dependent on dose and most of these patients had elevated levels prior to receiving Deferasirox. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). There have been post-marketing reports of hepatic failure in patients treated with Deferasirox. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.
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 Special warnings and precautions for use).
The following adverse drug reactions, listed in Table 5, have been reported following treatment with Deferasirox dispersible tablet. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

Tabulated summary of adverse drug reactions
Table 5 Adverse drug reactions

Psychiatric disorders	
Uncommon:	anxiety, sleep disorder
Nervous system disorders	
Common:	headache
Uncommon:	dizziness
Eye disorders	
Uncommon:	cataract, maculopathy
Rare:	optic neuritis
Ear and labyrinth disorders	
Uncommon:	deafness
Respiratory, thoracic and mediastinal disorders	
Uncommon:	laryngeal pain
Gastrointestinal disorders	
Common:	diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis
Rare:	oesophagitis
Hepatobiliary disorders	
Common:	transaminases increased
Uncommon:	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritus
Uncommon:	pigmentation disorder
Rare:	erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	
Very common:	blood creatinine increased
Common:	proteinuria
Uncommon:	renal tubular disorder (Fanconi syndrome)
General disorders and administration site conditions	
Uncommon:	pyrexia, oedema, fatigue

Listing of Adverse drug reactions from post-marketing spontaneous reports
Spontaneously reported adverse reactions, presented in Table 6, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

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

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

Description of selected adverse drug reactions
Cytopenias
There have been post-marketing reports of cytopenias including neutropenia, thrombocytopenia, and aggravated anemia in patients treated with Deferasirox. Most of these patients had pre-existing hematologic disorders that are frequently associated with bone marrow failure (see section Special warnings and precautions for use). The relationship of these episodes to treatment with Deferasirox is uncertain.

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

Pediatric population
Renal tubulopathy has been reported in patients treated with Deferasirox. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 µg/L.

4.9 Overdose
Single doses up to 40 mg/kg of the Deferasirox dispersible tablet formulation (corresponding to a dose of 28 mg/kg Irosix Film Coated Tablets) in normal subjects have been well tolerated.
Early signs of acute overdose are digestive effects such as abdominal pain, diarrhea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.
There is no specific antidote for Deferasirox. Standard procedures for management of overdose (e.g. induction of emesis or gastric lavage) may be indicated as well as symptomatic treatment, as medically appropriate.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Mechanism of action
Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the feces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.
Pharmacodynamics
In an iron balance metabolic study in iron overloaded adult thalassemic 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.
Deferasirox has been investigated in adult and pediatric patients (aged 2 years and older) with chronic iron overload due to blood transfusions. The underlying conditions requiring transfusion included beta-thalassemia, sickle cell disease, and other congenital and acquired anemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anemia and other very rare anemias).
Daily treatment with the Deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and pediatric patients with beta-thalassemia 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) 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 anemias. 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 (see section Posology and method of administration). Serum ferritin assessed by monthly monitoring reflected changes in liver iron concentration indicating that trends in serum ferritin can be used to monitor response to therapy.
In patients with cardiac iron deposition (MRI T2* <20 ms), treatment with Deferasirox was shown to remove cardiac iron as demonstrated by progressive improvements in T2* values over 3 years of observation. In patients without cardiac deposition, Deferasirox was shown to prevent clinically relevant cardiac iron deposition (maintenance of T2* at >20 ms) over 1 year of observation, despite significant ongoing transfusion exposure.
In patients with non-transfusion-dependent thalassemia syndromes and iron overload, treatment with Deferasirox at a dose of 10 mg/kg/day (dispersible tablet formulation) for one year led to a reduction in mean liver iron concentration from baseline by -3.80 mg Fe/g dw, while an increase of 0.38 mg Fe/g dw was observed in patients treated with placebo. In addition, treatment with Deferasirox at a dose of 10 mg/kg/day (dispersible tablet formulation) for one year led to a reduction in mean serum ferritin from baseline by -222.0 µg/L, while an increase of 114.5 µg/L was observed in patients treated with placebo.

5.2 Pharmacokinetic properties
Irosix Film Coated Tablets are a strength-adjusted formulation of Deferasirox with higher bioavailability compared to the Deferasirox dispersible tablets formulation. After strength-adjustment, the film-coated 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%).
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) was about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been determined. Bioavailability of Deferasirox with Irosix Film Coated Tablets was 36% greater than that with Deferasirox 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 Irosix Film Coated Tablets should be taken either on an empty stomach or with a light meal.
Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 L in adults.
Biotransformation
Glucuronidation is the main metabolic pathway for Deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalysed (oxidative) metabolism of Deferasirox appears to be minor in humans (about 8%). No inhibition of Deferasirox metabolism by hydroxyurea was observed *in vitro*. Deferasirox undergoes enterohepatic recycling. In a healthy volunteer study, the administration of cholestyramine after a single dose of Deferasirox resulted in a 45% decrease in Deferasirox exposure (AUC).
Elimination
Deferasirox and its metabolites are primarily excreted in the feces (84% of the dose). Renal excretion of Deferasirox and its metabolites is minimal (8% of the dose). The mean elimination half-life ($T_{1/2}$) ranged from 8 to 16 hours.
Linearity/non-linearity
The C_{max} and AUC_{0-24h} of Deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3.
Special populations
Pediatric patients
The overall exposure of adolescents (12 to ≤17 years) and children (2 to <12 years) to Deferasirox after single and multiple doses was 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 has not been studied in elderly patients (aged 65 or older).
Renal or hepatic impairment
The pharmacokinetics of Deferasirox has not been studied in patients with renal impairment.
The average AUC of Deferasirox in 6 subjects with mild hepatic impairment (Child-Pugh A) increased 16% over that found in 6 subjects with normal hepatic function, while the average AUC of Deferasirox in 6 subjects with moderate hepatic impairment (Child-Pugh B) increased 76% over that found in 6 subjects with normal hepatic function. The average C_{max} of Deferasirox in subjects with mild or moderate hepatic impairment increased 22% over that found in subjects with normal hepatic function. The impact of severe hepatic impairment (Child-Pugh C) was assessed in only one subject (see section Posology and method of administration and section Special warnings and precautions for use). The pharmacokinetics of Deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
Microcrystalline Cellulose, Crospovidone, Povidone, Poloxamer, Magnesium Stearate
Film-coat:
Opadry Complete Film Coating System 00F505009 Blue (360mg), Opadry Complete Film Coating System 00F505008 Blue (180mg), Opadry Complete Film Coating System 00F505007 Blue (90mg)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to the expiry date on the product labels.

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

6.5 Nature and contents of container
Clear PVC/PVDC/Alu blisters in cartons of 1 × 10's, 3 × 10's, 6 × 10's, 10 × 10's, 50 × 10's and 100 × 10's (90mg and 360mg). 30's tablets in 40cc HDPE bottle pack (180mg). Not all packs sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MANUFACTURER

Manufactured by:
Novugen Pharma (Malaysia) Sdn.Bhd.
No.27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
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8 DATE OF REVISION
15/04/2022

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