Pharmacode position will vary as per width of PI

FRONT SIDE

340.00 mm

610.00 mm

Space for Pharma Code

Feronock 90/180/360 Artwork Code

Package Insert

Feronock 90,180 and 360 Deferasirox 90,180 and 360 mg Film Coated Tablets

Product Description:
Deferasirox 90 mg Film Coated Tablets are White to off white in color, film-coated, oval biconvex tablet with beveled edges, debossed with '144' on one side and plain on the other side.

Deferasirox 180 mg Film Coated Tablets are Light blue to blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with '145' on one side and plain on the other side.

Deferasirox 360 mg Film Coated Tablets are Blue to dark blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with '146' on one side and plain on the other side.

Composition:
Feronock 90 (Deferasirox 90mg Film Coated Tablets)
Each film coated tablet contains:
Deferasirox Ph.Eur. …… 90 mg
Excipients.....q.s.
Opadry Blue CFCS 03F505169

Feronock 180 (Deferasirox 180mg Film Coated Tablets)
Each film coated tablet contains:
Deferasirox Ph.Eur. …… 180 mg
Excipients.....q.s.
Opadry Blue CFCS 03F505165

Feronock 360 (Deferasirox 360mg Film Coated Tablets)
Each film coated tablet contains:
Deferasirox Ph.Eur. …… 360 mg
Excipients.....q.s.
Opadry Blue CFCS 03F505166

Inactive ingredients:
Feronock 90
Lactose Monohydrate (Pharmatose 200 M), Crospovidone (polyplasdoneXL) , Povidone (Kollidon 30), Poloxamer 188 (Kollidon P 188) , Lactose Monohydrate (Super Tab 11 SD), Crospovidone (polyplasdoneXL), Magnesium Stearate , Colloidal SiO2 Aerosil 200 Pharma , Opadry Blue -CFCS 03F505169

Feronock 180
Lactose Monohydrate (Pharmatose 200 M), Crospovidone (polyplasdoneXL) , Povidone (Kollidon 30), Poloxamer 188 (Kollidon P 188) , Lactose Monohydrate (Super Tab 11 SD), Crospovidone (polyplasdoneXL), Magnesium Stearate , Colloidal SiO2 Aerosil 200 Pharma , Opadry Blue -CFCS 03F505165

Feronock 360
Lactose Monohydrate (Pharmatose 200 M), Crospovidone (polyplasdoneXL) , Povidone (Kollidon 30), Poloxamer 188 (Kollidon P 188) , Lactose Monohydrate (Super Tab 11 SD), Crospovidone (polyplasdoneXL), Magnesium Stearate , Colloidal SiO2 Aerosil 200 Pharma , Opadry Blue -CFCS 03F505166

Excipient with known effect:
90 mg: Ech film coated tablets contains 36.85 mg lactose monohydrate.
180 mg: Ech film coated tablets contains 73.70 mg lactose monohydrate.
360 mg: Ech film coated tablets contains 147.40 mg lactose monohydrate.

CLINICAL PHARMACOLOGY
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 (PD)
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 microgram/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. 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 microgram/L, while an increase of 114.5 microgram/L was observed in patients treated with placebo.

Pharmacokinetics (PK)
Deferasirox 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 Cmax was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis has 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 (Tmax) 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 Deferasirox 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 Cmax were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and Cmax were increased (by 18% and 29%, respectively). The increases in Cmax 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 Deferasirox 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 (T1/2) ranged from 8 to 16 hours.

Linearity / non-linearity
The C_{max} and AUC0-24h 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 Cmax 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. The pharmacokinetics of deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

Indications:
Feronock film-coated tablet is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).
Feronock film-coated tablet is also indicated for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and over.

Dosage and administration:
Transfusional iron overload
Dosage regimen
It is recommended that therapy with Deferasirox 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 microgram/L). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.
Deferasirox 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 Deferasirox film-coated tablets, the dose of Deferasirox 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 Deferasirox 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 Deferasirox 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 Deferasirox film-coated tablets).

Dose adjustment
It is recommended that serum ferritin be monitored every month and that the dose of Deferasirox 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 level persistently above 2500 microgram/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 microgram/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. If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

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

Table 1 Transfusional iron overload: Recommended doses Deferasirox Dispersible tablets

	Deferasirox Dispersible tablets	Deferasirox 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 >1000 microgram/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: 5 to 10 mg/kg/day Up to 40 mg /kg/day	Increase: 3.5 to 7 mg/kg/day Up to 28 mg/kg/day		>2,500 microgram/L
	Decrease: 5 to 10 mg/kg/day When target is reached	Decrease: 3.5 to 7 mg/kg/day		500 to 1,000 microgram/L
Maximum dose	40 mg/kg/day	28 mg/kg/day		
Consider dose interruption				<500 microgram/L

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

Non-transfusion-dependent thalassemia (NTDT) syndromes
Dosage
Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) or serum ferritin consistently >800 microgram/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of overchelation. Deferasirox 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 Deferasirox film-coated tablets, the dose of Deferasirox 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 Deferasirox 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. 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 microgram/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 microgram/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 microgram/L.

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

The corresponding recommended doses for both formulations are shown in Table 2

Table 2 NTDT: Recommended doses

	Deferasirox Dispersible tablets	Deferasirox 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 micro gram/L
Adjustment Steps	Increase		≥7 mg Fe/g dw	or	>2,000 micro gram/L
(every 3 to 6 month)	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day	<7 mg Fe/g dw	or	>2,000 micro microgram/L
	Decrease				
	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	≤2000 micro gram/L
	For pediatric patients				
Dose Interruption			<3 mg Fe/g dw	or	<300 micro gram/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 for Deferasirox Dispersible tablets	Daily dose for Deferasirox 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
Deferasirox 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.

Patients with hepatic impairment
Deferasirox has been studied in a clinical trial in subjects with hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50%. Deferasirox film-coated tablets should not be used in patients with severe hepatic impairment (Child-Pugh C). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter.

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. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

Elderly patients
The dosing recommendations for elderly patients are the same as described above. In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment.

Instructions for Use
The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, Feronock 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.

Feronock 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.

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.

Warnings and Precautions:
The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.
Caution should be used in elderly patients due to a higher frequency of adverse reactions.

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

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. A study which assessed the renal function of patients enrolled in the registration studies up to 13 years later, confirmed the non-progressive nature of these serum creatinine observations.

Cases of acute renal failure have been reported following the post-marketing use of deferasirox. Although causal relationship with Deferasirox 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 microgram/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.

BACK SIDE

340.00 mm

610.00 mm

For adult patients, the daily dose of Deferasirox 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. 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, Deferasirox film-coated tablets should be interrupted. Therapy with Deferasirox 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 (Deferasirox 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 dose 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
Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh C). 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.

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials. 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. 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, Deferasirox 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 Deferasirox 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. 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 Deferasirox film-coated tablets should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with Deferasirox film-coated tablets may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal Disorders
Gastrointestinal irritation may occur during Deferasirox 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. 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 Deferasirox film-coated tablets in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants 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. If reactions are severe, Deferasirox film-coated tablets should be discontinued and appropriate medical intervention instituted. Deferasirox 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 Deferasirox film-coated tablets should be discontinued immediately and should not be reintroduced.

Rare cases of erythema multiforme have been reported during Deferasirox film-coated tablets treatment.

Skin rashes may appear during Deferasirox film-coated tablets treatment. For rashes of mild to moderate severity, Deferasirox 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, Deferasirox 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. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Deferasirox 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.

Deferasirox has not been associated with growth retardation in children followed for up to 5 years in clinical trials with the dispersible tablet formulation. However, as a general precautionary measure, body weight and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

Driving and using 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.

ADVERSE DRUG REACTIONS:

Summary of the safety profile

In clinical trials 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.

In clinical trials of the 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.

In a 1-year, randomized, double-blind, placebo-controlled study of the deferasirox dispersible tablet formulation in patients with non-transfusion-dependent thalassemia syndromes and iron overload, diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events reported by patients receiving 10 mg/kg/day (dispersible tablet formulation). Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8%, respectively, of patients receiving 10 mg/kg/day deferasirox. 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 treated with 10 mg/kg/day (dispersible tablet formulation).

As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.

The following adverse drug reactions, listed in Table 5, have been reported in clinical studies following treatment with deferasirox dispersible tablet. Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated summary of adverse drug reactions from clinical trials

Table 5 Adverse drug reactions reported in clinical studies 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

In a study to assess the safety of deferasirox film-coated and dispersible tablets, 173 adult and pediatric patients with transfusion-dependent thalassemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed.

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 (both spontaneous and from clinical trials) 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. 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 microgram/L.

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) with transfusional hemosiderosis received deferasirox, there were no unexpected safety findings regarding adverse events (AEs) or laboratory abnormalities. Increases in serum creatinine of >33% and above the upper limit of normal (ULN) on ≥2 consecutive occasions were observed in 3.1% of children and elevation of alanine aminotransferase (ALT) greater than 5 times the ULN was reported in 4.3% of children. The most frequently observed AEs with reported suspected relationship to study drug were increase in ALT (21.1%), increase in aspartate aminotransferase (AST, 11.9%), vomiting (5.4%), rash (5.0%), increase in blood creatinine (3.8%), abdominal pain (3.1%) and diarrhoea (1.9%). Overall growth and development were not affected in this pediatric population.

Interaction with other Medicaments

Agents that may decrease deferasirox systemic exposure
In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% to 51%). Therefore, the concomitant use of Deferasirox film-coated tablets with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Deferasirox film-coated tablets efficacy. If Deferasirox film-coated tablets and a potent UGT inducer are used concomitantly, increases in the dose of Deferasirox film-coated tablets should be considered based on clinical response to therapy.

Interaction with food
The Cmax of deferasirox film-coated tablets was moderately 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.
Interaction with midazolam and other agents metabolized by CYP3A4
In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablet and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% to 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 metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

Interaction with repaglinide and other agents metabolized by CYP2C8
In a healthy volunteer study, the concomitant administration of deferasirox (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP2C8 substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide AUC and Cmax by 131% (90% CI: 103% to 164%) and 62% (90% CI: 42% to 84%), respectively. 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
In a healthy volunteer study, the concomitant administration of deferasirox (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84% (90% CI: 73% to 95%). The single dose Cmax was not affected, but an increase of theophylline Cmax is expected to occur with chronic dosing. 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
Based on literature reports, 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) observed in clinical trials, post-marketing experience or published literature (as applicable) 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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL:

Pregnancy
Risk summary
No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown.

As a precaution, it is recommended that Deferasirox film-coated tablets not be used during pregnancy unless clearly necessary.

Data
Animal data
The potential for toxicity to reproduction was assessed in rats and rabbits.

Those studies showed that 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.

Lactation
Risk summary
It is not known if deferasirox is transferred into human milk.
In animal studies, deferasirox was found to be rapidly and extensively transferred into maternal milk. No effects on the offspring were noted at maternally non-toxic doses of deferasirox. Breast-feeding while taking Deferasirox 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.

Infertility
Deferasirox did not affect fertility or reproduction in rat studies even at toxic doses.

Overdose:

Single doses up to 40 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 28 mg/kg Deferasirox 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.

Shelf life:
24 months

Storage Condition:
Store below 30°C. Store in the original package in order to protect from light and moisture.
Keep out of reach of children.

PRESENTATION:
Aluminium Foil and clear transparent PVC/PVDC Blister pack
Blister of 10 tablets
Box containing 30 Tablets
Read the instruction carefully before use

Manufactured by:
Inventia
Inventia Healthcare Limited
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East), Thane 421506,
Maharashtra State, India

Product Registration Holder in Malaysia
HEALOL PHARMACEUTICALS SDN. BHD.
74-3, Jalan Wangsa Delima 6, KLSC Wangsa Maju,
53300 Kuala Lumpur, Malaysia.

Date of Revision of Package Insert:
Oct. 2025

B-0007/02

Product Name: Feronock 90,180 and 360 Deferasirox 90,180 and 360 mg Film Coated Tablets		**Packaging Material:** Booklet (Front & Back Side)		**Location:** Ambernath
Dimension: 340 x 610 mm (As per Drawing)		**Artwork No.:** B-0007/02		**SAP Code:**
Drawing No.: PGB195251039 & PGB195251040 BK		**Pharma Code:**		**Country/Client:** Malaysia_Healol
Substrate: ITC Superfine Paper		**Specification:** 40 GSM		**Pack Size:** 30 Tablets
Any other Requirement: Folding Size : 30 x 76 &Transparency Required Booklet to be closed with tear here adhesive tape				
No. of Colour: 01 ■ Black				
Version No.: 1.0	**Change History :** 1) As per RA mail 09-10-2025			**Date:** 27-10-2025
Signature and Date				
Department	**Client**	**Packaging Development - R&D**	**Regulatory Affairs**	**Corporate Quality**