Important Information to Remember About Toxefro® (Deferasirox) Physician guide

Toxefro® 250 mg Dispersible Tablets
Toxefro® 500 mg Dispersible Tablets
Toxefro® 90mg F.C Tablets
Toxefro® 180mg F.C Tablets
Toxefro® 360mg F.C Tablets

www.mspharma.com

Objectives

This educational material is essential to ensure the safe and effective use of the product and provides detailed information on posology and required monitoring of patients being treated with deferasirox, to minimize potential safety risks.
please advised to be read carefully before prescribing/dispensing/administering the product.

Indication

Chronic Transfusional Iron Overload

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-thalassemia major aged 6 years and older.

Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- In pediatric patients with beta-thalassemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years
- In adult and pediatric patients with beta-thalassemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older
- In adult and pediatric patients with other anemias aged 2 years and older

Non–Transfusion-Dependent Thalassemia

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 thalassemia syndromes aged 10 years and older.

Contraindications

- Deferasirox is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients
- Deferasirox is contraindicated for use in combination with other iron chelator therapies as the safety of such combinations has not been established
- Deferasirox is contraindicated in patients with estimated CrCl <60 ml/min
  - Deferasirox has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min

Starting Deferasirox treatment

Before initiating therapy

Pretreatment Measures	
Test	**Pretreatment**
SF	✓
LIC[a]	✓
Serum creatinine	2x
CrCl and/or plasma cystatin C	✓
Proteinuria	✓
Serum transaminase (ALT and AST)	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight and height	✓
and sexual development (pediatric patients)	✓

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; LIC, liver iron concentration; SF, serum ferritin.

[a] For non–transfusion-dependent thalassemia (NTDT) patients: Measure iron overload with LIC. For patients with NTDT, LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimize the risk of overchelation in all patients.

Dose comparisons between Deferasirox film-coated tablets and dispersible tablets

There are different formulations of Toxefro® (Deferasirox): Toxefro® (Deferasirox) film-coated tablets and Toxefro® (Deferasirox) dispersible tablets.

- Film-coated tablets: 90 mg, 180 mg, and 360 mg
- Dispersible tablets: 250 mg, and 500 mg

All formulations have the same active ingredient (Deferasirox).

- Toxefro® (Deferasirox) film-coated tablets are a strength-adjusted formulation of Toxefro® (Deferasirox), with higher bioavailability than the dispersible tablets
- Formulations are differentiated by form and/or color and/or size and/or packaging

A different posology and method of administration must be applied when switching patients from dispersible tablets to film-coated tablets of Toxefro® (Deferasirox) .

Important differences between Toxefro® (Deferasirox) film-coated tablets, and dispersible tablets

Toxefro® (Deferasirox) film-coated tablets			
Strengths: 90 mg 180 mg 360 mg	May be taken on an empty stomach or with a light meal Tablets can be swallowed whole with some water. For patients who are unable to swallow whole tablets, Toxefro® (Deferasirox) film-coated tablets may be crushed and administered by sprinkling onto soft food (eg, yogurt or applesauce)	Does not contain lactose	  
Toxefro® (Deferasirox) dispersible tablets			
Strengths: 250 mg 500 mg	Must be taken on an empty stomach, at least 30 minutes before food Disperse tablets in water, orange juice, or apple juice. Dispersible tablets must not be chewed or swallowed whole	Contains lactose	 

Converting from dispersible tablets to film-coated tablets

The dose of the film-coated tablets should be 30% lower than the dose of dispersible tablets, rounded to the nearest whole film-coated tablet.

To avoid dosing errors, it is important that the prescription specify both the type of formulation (dispersible tablet or film-coated tablet) and the calculated dose per day with strength of film-coated tablets or dispersible tablets.
With the availability of a film-coated tablet formulation of Deferasirox

Dose comparisons between Deferasirox film-coated tablets and dispersible tablets

Deferasirox film-coated tablets	Deferasirox dispersible tablets
Dose range: 7-28 mg/kg/day; calculated and rounded to the nearest whole tablet size	Dose range: 10-40 mg/kg/day; calculated and rounded to the nearest whole tablet size
Dose adjustment: increments of 3.5-7 mg/kg/day	Dose adjustment: increments of 5-10 mg/kg/day
Therapeutic dose range: 7 mg/kg/day 14 mg/kg/day (maximum recommended dose for NTDT patients) 21 mg/kg/day 28 mg/kg/day (maximum recommended dose for transfusional iron overload patients)	Therapeutic dose range: 10 mg/kg/day 20 mg/kg/day (maximum recommended dose for NTDT patients) 30 mg/kg/day 40 mg/kg/day (maximum recommended dose for transfusional iron overload patients)
Calculated daily dose example for 50 kg patient with transfusional iron overload receiving 21 mg/kg/day: 21 mg/kg/day × 50 kg= 1050 mg/day Three (3) 360 mg tablets	Calculated daily dose example for 50 kg patient with transfusional iron overload receiving 30 mg/kg/day: 30 mg/kg/day × 50 kg = 1500 mg/day Three (3) 500 mg tablets

Deferasirox film-coated tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 14 mg/kg/day body weight
- Doses >28 mg/kg/day are not recommended
- Monitor your patients regularly

Deferasirox film-coated tablets starting dose and dose adjustment for patients with transfusional iron overload

INITIATE therapy	**UP-TITRATE** to achieve target SF when necessary[a]	**DOWN-TITRATE** to avoid overchelation	**INTERRUPTION** Consider interruption once target SF has been achieved
14 mg/kg body weight per day (recommended starting dose) 20 U (~100 ml/kg) PRBCs or SF >1000 µg/l	Increase in increments of 3.5 to 7 mg/kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF=500-1000 µg/l, or closely monitor renal and hepatic function and serum ferritin levels	SF consistently <500 µg/l
7 mg/kg body weight per day <7 ml/kg/month of PRBCs (~ <2 units/month for an adult)	Increase in increments of 3.5 to 7 mg/kg/day	----------	
21 mg/kg body weight per day >14 ml/kg/month of PRBCs (~ >4 units/month for an adult)	Increase in increments of 3.5 to 7 mg/kg/day Consider alternative treatment options if no satisfactory control is achieved at doses >28 mg/kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time, or closely monitor renal and hepatic function and serum ferritin levels	
Patients already well managed on treatment with deferoxamine A starting dose of Deferasirox film-coated tablets that is numerically one third that of the deferoxamine dose could be considered	Increase in increments of 5 to 10 mg/kg/day if dose is <20 mg/kg body weight per day and sufficient efficacy is not obtained	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time, or closely monitor renal and hepatic function and serum ferritin levels	

PRBCs, packed red blood cells; U, units.

[a] In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric transfusional iron overload patients

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

Deferasirox film-coated tablets dosing for patients with non–transfusion-dependent thalassemia (NTDT)

- Recommended initial dose: 7 mg/kg/day body weight
- Doses >14 mg/kg/day are not recommended
- Only one course of treatment with Deferasirox is recommended for patients with NTDT
- Monitor your patients regularly

Deferasirox film-coated tablets starting dose and dose adjustment for patients with non—transfusion-dependent thalassemia			
INITIATE therapy	**UP-TITRATE** to achieve target SF when necessary[a,b]	**DOWN-TITRATE** to avoid over-chelation	**STOP** therapy once target SF has been achieved
7 mg/kg/day	Increase in increments of 3.5 to 7 mg/kg/day	Decrease dose to7 mg/ kg/day or less, or closely monitor renal and hepatic function and serum ferritin levels	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 ≥5 mg Fe/g dw OR SF consistently >800 µg/l	LIC ≥7 mg Fe/g dw OR SF consistently >2000 µg/lb	LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l	**GOAL LIC <3 mg Fe/g dw OR SF consistently <300 µg/l**

dw, dry weight; LIC, liver iron concentration; SF, serum ferritin.
[a]Doses above 20 mg/kg/day are not recommended for patients with NTDT. In patients in whom LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 10 mg/kg.
[b]In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric NTDT patients

In pediatric patients, dosing should not exceed 7 mg/kg/day. LIC should be monitored every 3 months when SF is .800 µg /l in order to avoid overchelation.
WARNING: Data in children with NTDT are very limited. As a consequence, Deferasirox therapy should be closely monitored to detect side effects and to follow iron burden in the pediatric population. A single course of treatment is proposed for NTDT patients. In addition, before administering Deferasirox to heavily iron-overloaded children with NTDT, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Deferasirox dispersible tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 20 mg/kg/day body weight
- Doses >28 mg/kg/day are not recommended
- Monitor your patients regularly

Deferasirox dispersible tablets starting dose and dose adjustment for patients with transfusional iron overload

INITIATE therapy	**UP-TITRATE** to achieve target SF when necessary[a]	**DOWN-TITRATE** to avoid over-chelation	**INTERRUPTION** Consider interruption once target SF has been achieved
20 mg/kg body weight per day (recommended starting dose) 20 U (~100 ml/kg) PRBCs or SF >1000 µg/l	Increase in increments of 3.5 to 7 mg/kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF=500-1000 µg/l, or closely monitor renal and hepatic function and serum ferritin levels	SF consistently <500 µg/l
7 mg/kg body weight per day <7 ml/kg/month of PRBCs (~ <2 units/month for an adult	Increase in increments of 3.5 to 7 mg/kg/day	----------	
21 mg/kg body weight per day >14 ml/kg/month of PRBCs (~ >4 units/month for an adult)	Increase in increments of 3.5 to 7 mg/kg/day Consider alternative treatment options if no satisfactory control is achieved at doses >28 mg/ kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time, or closely monitor renal and hepatic function andserum ferritin levels	
Patients already well managed on treatment with deferoxamine Starting dose of Deferasirox dispersible tablets that is numerically half that of the deferoxamine dose	Increase in increments of 5 to 10 mg/kg/day if dose is <20 mg/kg body weight per day and sufficient efficacy is not obtained	Decrease dose in steps of 5 to 10 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time, or closely monitor renal and hepatic function and serum ferritin levels	

PRBCs, packed red blood cells; U, units.

[a] In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric transfusional iron overload patients

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

Deferasirox dispersible tablets dosing for patients with non–transfusion-dependent thalassemia (NTDT)

- Recommended initial dose: 10 mg/kg/day body weight
- Doses >20 mg/kg/day are not recommended
- Only one course of treatment with Deferasirox is recommended for patients with NTDT
- Monitor your patients regularly

Deferasirox dispersible tablets starting dose and dose adjustment for patients with non—transfusion-dependent thalassemia			
INITIATE therapy	**UP-TITRATE** to achieve target SF when necessary [a]	**DOWN-TITRATE** to avoid over-chelation	**STOP** therapy once target SF has been achieved
10 mg/kg/day	Increase in increments of 5 to 10 mg/kg/day	Decrease dose to 10 mg/kg/day or less, or closely monitor renal and hepatic function and serum ferritin levels	Retreatment is not recommended for patients with NTDT
LIC ≥5 mg Fe/g dw OR SF consistently >800 µg/l	LIC ≥7 mg Fe/g dw OR SF consistently >2000 µg/lb	LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l	**GOAL LIC <3 mg Fe/g dw OR SF consistently <300 µg/l**

dw, dry weight; LIC, liver iron concentration; SF, serum ferritin.
[a] Doses above 20 mg/kg/day are not recommended for patients with NTDT. In patients in whom LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 10 mg/kg.
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Pediatric NTDT patients

In pediatric patients, dosing should not exceed 10 mg/kg/day. LIC should be Monitored every 3 months when SF is ≤800 µg/l in order to avoid over-chelation. WARNING: Data in children with NTDT are very limited. As a consequence, Deferasirox therapy should be closely monitored to detect side effects and to follow iron burden in the pediatric population. A single course of treatment is proposed for NTDT patients. In addition, before administering Deferasirox to heavily iron-overloaded children with NTDT, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Considerations for treatment interruption of Deferasirox

Consideration	Conditions for treatment interruption or discontinuation
SF	Consistently <500 µg/l (in transfusional iron overload) or <300 µg/l (in NTDT syndromes)
Serum creatinine/ Creatinine clearance	Adult and pediatric: after dose reduction, when serum creatinine remains >33% above baseline and/or CrCl <LLN (90 ml/min)—also refer patient to renal specialist and consider biopsy
Proteinuria	Persistent abnormality—also refer patient to renal specialist and consider biopsy
Tubular markers	Abnormalities in levels of tubular markers and/or if clinically indicated—also refer patient to renal specialist and consider biopsy (also consider dose reduction)
Serum transaminase	Persistent and progressive increase in liver enzyme
Metabolic acidosis	Development of metabolic acidosis
SJS, TEN, DRESS, or any other SCAR	Suspicion of any Severe Cutaneous Adverse Reaction (SCAR): discontinue immediately and do not reintroduce
Hypersensitivity reactions (eg, anaphylaxis, angioedema)	Occurrence of reaction: discontinue and institute appropriate medical intervention. Do not reintroduce in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock
Vision and hearing	Disturbances of vision or hearing (also consider dose reduction)
Unexplained cytopenia	Development of unexplained cytopenia

DRESS, drug reaction with eosinophilia and systemic symptoms; LLN, lower limit of normal; SCAR, serious cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Monitoring recommendations for patients prior to and during Deferasirox treatment

	Baseline	In the first month after initiation of Deferasirox or after dose modification	Monthly	Every 3 months	Yearly
SF	✓		✓		
LIC[a]	✓			✓ (for pediatric patients only, if SF is ≤800 µg/l)	
Serum creatinine	**2x**	**Weekly** (Should also be tested weekly in the first month after dose modification)	✓		
Creatinine clearance and/or plasma cystatin C	✓	**Weekly** (Should also be tested weekly in the first month after dose modification)	✓		
Proteinuria	✓		✓		
Serum transaminases, bilirubin, alkaline phosphatase	✓	**Every 2 weeks**	✓		
Body weight and height	✓				✓
Auditory/ophthalmic testing (including funduscopy)	✓				✓
sexual development	✓				✓

[a] For non–transfusion-dependent thalassemia (NTDT) patients: Measure iron overload with LIC. For patients with NTDT, LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimize the risk of overchelation in all patients.

The results of the tests for serum creatinine, CrCl, plasma cystatin C, proteinuria, SF, liver transaminases, bilirubin, and alkaline phosphatase should be recorded and regularly assessed for trends. The results should also be noted in the patient's medical records, along with pretreatment baseline levels for all test

Renal safety profile

Findings from clinical trials

Parameters measured in clinical trials

In Deferasirox clinical trials, only patients with a serum creatinine within the normal range for their age and gender were enrolled. The individual baseline value of serum creatinine was calculated as the average of two (and for some patients three) pretreatment values of serum creatinine. The mean intra-patient coefficient of variation of these two or three pretreatment measurements was approximately 10%.This is why duplicate serum creatinine values are recommended before initiating treatment with Deferasirox . During treatment, serum creatinine was monitored monthly, and when indicated, dose adjustments were made for increases of serum creatinine as described below.

Results from the one-year core studies

During clinical trials, 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. Indeed, in some cases, only a stabilization of the serum creatinine values has been observed after dose reduction.

Monitoring serum creatinine and CrCl

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, CrCl** (estimated with the Cockcroft-Gault or Modification of Diet in Renal Disease 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.**

Methods for estimating CrCl

For your reference, here is a brief overview of methods to estimate CrCl in adults and children when prescribing Deferasirox.

Adult

Once a method has been selected, you should not interchange between formulas.

Cockcroft–Gault formula

The Cockcroft-Gault formula employs creatinine measurements and the patient's

weight to predict CrCl.

The formula states CrCl in ml/min

Creatinine clearance = (140 – age) × weight (kg)/72[a] × serum creatinine (mg/100 ml). ***In female patients, creatinine clearance is multiplied by 0.85.***

CKD-EPI equation
A general practice and public health perspective favors adoption of the CKD-EPI equation in North America, Europe, and Australia and using it as a comparator for new equations in all locations.
Glomerular filtration rate (GFR) = 141 x min(Scr/κ ,1) $^{\alpha}$ x max(Scr/ κ,1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black], where **Scr** is serum creatinine, **κ** is 0.7 for females and 0.9 for males, **α** is -0.329 for females and -0.411 for males, **min** indicates the minimum of Scr/ κ or 1, and **max** indicates the maximum of Scr/ κ or 1.

Pediatric
Schwartz formula
Creatinine clearance (ml/min) = constant[b] × height (cm)/ serum creatinine (mg/dl)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[a] If serum creatinine is provided in mmol/l instead of mg/dl, the constant should be 815 instead of 72.
[b] The constant is 0.55 in children and adolescent girls or 0.70 in adolescent boys.

Renal monitoring and actions
Deferasirox film-coated tablets: Reduce the dose by 7 mg/kg/day, if Deferasirox dispersible tablets: Reduce the dose by 10 mg/kg/day, if **• Adult: serum creatinine >33% above baseline and CrCl <LLN (90 ml/min) at two consecutive visits and cannot be attributed to other causes** • Pediatric: serum creatinine either above age-appropriate ULN and/or CrCl falls to <LLN (<90 ml/min) at two consecutive visits and cannot be attributed to other causes.
Interrupt treatment after dose reduction if **• Serum creatinine remains >33% above baseline, and/or** • CrCl <LLN (<90 ml/min)
Monitoring and action of renal tubular function **• 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)** **• Consider dose reduction or interruption if there are abnormalities** **• Renal tubulopathy has been mainly reported in children and adolescents with** β-thalassemia treated with Deferasirox
Refer patient to a renal specialist and consider renal biopsy • When serum creatinine is significantly elevated and if another abnormality has been detected (eg, proteinuria, signs of Fanconi syndrome) despite dose reduction or interruption
Patients with preexisting renal conditions and patients who are receiving medicinal products that depress renal function may be at greater risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting
Pediatric patients with thalassemia may be at greater risk for renal tubulopathy (particularly metabolic acidosis)
Consider hyperammonemic encephalopathy and early measurement of ammonia levels if **• Patients develop unexplained changes in mental status while on Deferasirox** therapy, particularly in children

Hepatic safety profile

Liver function assessment
Liver function test elevations have been observed in patients treated with Deferasirox • Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with Deferasirox • Most reports of hepatic failure involved patients with significant morbidities including preexisting liver cirrhosis • However, the role of Deferasirox as a contributing or aggravating factor cannot be excluded
Monitor serum transaminases, bilirubin, and alkaline phosphatase before the initiation of treatment, every 2 weeks during the first month and monthly thereafter • Interrupt treatment if persistent and progressive increase in serum transaminase levels is noted
Recommendations in hepatic impairment
Deferasirox is not recommended in patients with preexisting severe hepatic disease (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%, 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
The pharmacokinetics of Deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range
Consider hyperammonemic encephalopathy and early measurement of ammonia levels if • Patients develop unexplained changes in mental status while on Deferasirox therapy, particularly in children

Call for reporting:

Additional copies of the materials can be obtained by contacting MS pharma for pharmaceuticals.
Report suspected adverse drug reactions associated with Toxefro® (Deferasirox) by contacting:

Pharmacovigilance Department at MS Pharma:

- Email: pharmacovigilance@mspharma.com
- Website: www.mspharma.com
- Phone No: + 966112790122 Ext. 6013

The National Pharmacovigilance Center (NPC): (Saudi food and drug authority)

- Email: npc.drug@sfda.gov.sa
- Call Center: 19999
- Website: https://ade.sfda.gov.sa/
- QR Code