Important Information for Healthcare Professionals to Remember About Deferasirox Treatment

Deferasirox beta 180mg Film-Coated Tablets (Deferasirox)

This booklet provides detailed information on posology and monitoring of patients on deferasirox, to minimise key adverse effects including ***Medication Errors*** *during treatment.*

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

Adverse events should be reported.

Contact details can be found at Dr. Reddy's Laboratories – Good Health Can't Wait (drreddys.com)

Alternatively these can be reported to postlicensing.medicinesauthority@gov.mt. or reported to rp@ejbusuttil.com.

Date of approval: 19/12/2022

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1. What is deferasirox?

Indications

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 β-thalassaemia major aged 6 years and older.

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

• In paediatric patients with β-thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years

• In adult and paediatric patients with β-thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older

• In adult and paediatric patients with other anaemias aged 2 years and older Non–Transfusion-Dependent Thalassaemia (NTDT)

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

Mechanism of action

Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Purpose of this booklet

This booklet is for prescribers of deferasirox. It provides detailed information on posology and required monitoring of patients being treated with deferasirox, to minimise potential safety risks.

For further copies, please contact DrReddys Pharmacovigilance Department on pharmacovigilance@betapharm.de. For full safety information, please refer to the deferasirox Summary of Product Characteristics.

2. Formulation and method of administration

Deferasirox is supplied as film-coated tablets which are available in three strengths

- 90 mg film-coated tablets
- 180 mg film-coated tablets
- 360 mg film-coated tablets

Deferasirox may be taken on an empty stomach or with a light meal.
Deferasirox should be swallowed whole with some water. For patients who are unable to swallow whole tablets, deferasirox may be crushed and administered by sprinkling onto soft food (eg, yoghurt or apple sauce (apple puree)). The dose should be immediately and completely consumed, and not stored for future use.
Deferasirox should be taken once a day, preferably at the same time each day.

3. Dosing per indication – important differences to minimise the potential for medication errors

3.1 Dosing for patients with non–transfusion-dependent thalassaemia (NTDT)

• Recommended initial dose of deferasirox: 7 mg/kg body weight/day
• Doses >14 mg/kg/day are not recommended1
• Only one course of treatment with deferasirox is recommended for patients with NTDT1
• Monitor your patients regularly to ensure proper treatment

Deferasirox: Starting dose and dose adjustment for patients with NTDT			
INITIATE	**UP-TITRATE to achieve target when necessary Monitor monthly**	**DOWN-TITRATE to avoid overchelation Monitor monthly**	**STOP chelation therapy once goal has been achieved**
7 mg/kg/day	Increase in increments of 3.5 to 7 mg/kg/day up to a maximum dose of 14 mg/kg/day for adult patients and 7 mg/kg/day for paediatric patients	Decrease dose to 7 mg/kg/day or less or closely monitor renal and hepatic function and serum ferritin levels	Re-treatment is not recommended for patients with NTDT
LICb ≥5 mg Fe/g dw OR SF consistently >800 µg/l	LICb ≥7 mg Fe/g dw OR SF consistently >2000 µg/lc	LIC<7mg Fe/g dw or SF consistently ≤2000 µg/l	GOAL LIC<3mg Fe7g dw or SF consistently <300 µg/l

Paediatric NTDT patients
In paediatric 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 paediatric 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.

3.2 Dosing for patients with chronic transfusional iron overload

• Recommended initial dose: 14 mg/kg body weight/day
• Doses >28 mg/kg/day are not recommended
• Monitor your patients regularly to ensure proper treatment

Deferasirox: Starting dose and dose adjustment for patients with transfusional iron overload			
INITIATE	**UP-TITRATE to achieve target when necessary Monitor monthly**	**DOWN-TITRATE to avoid overchelation Monitor monthly**	**STOP chelation therapy once goal 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 up to a maximum dose of 28 mg/kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF = 500 to 1000 or closely monitor renal and hepatic function and serum ferritin levels	SF consistently <500 µg/l
7 mg/kg body weight per day	Increase in increments of 3.5 to 7 mg/kg/day up to a maximum dose of 28 mg/kg/day		
21 mg/kg body weight per day	Increase in increments of 3.5 to 7 mg/kg/day up to a maximum dose of 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 Starting dose of deferasirox that is numerically one third that of the deferoxamine dose	Increase in increments of 3.5 to 7 mg/kg/day if dose is <14 mg/kg body weight per day and sufficient efficacy is not obtained	In patients treated with doses >21 mg/kg, 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	

Paediatric transfusional iron overload patients

• The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional
iron overload are the same as for adult patients. Changes in weight of paediatric patients over time must be taken into account when calculating the dose

• In children with transfusional iron overload aged between 2 and 5 years, exposure is lower
than in adults. 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

• It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimise the risk of overchelation.

4. Safety and important monitoring requirements

4.1 Unknown consequences of long-term use in paediatric patients

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 paediatric population. 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. In paediatric patients with NTDT, dosing should not exceed 7 mg/kg/day. Liver iron concentration (LIC) should be monitored every 3 months when SF is ≤800 µg/l in order to avoid overchelation. Body weight, height and sexual development testing should be conducted annually in paediatric patients.

4.2 Dose-dependent rise in serum creatinine

Monitoring serum creatinine and creatinine clearance (CrCl)
Deferasirox may cause serious kidney problems, which can be fatal. Therefore, 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, 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 change between or interchange 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

$$\text{Estimated creatinine clearance in ml/minute} = \frac{(140 - \text{age}) \times \text{weight} \times \text{Constant}}{\text{Serum creatinine}}$$

Age = Years Weight = Ideal Body Weight In Kg Serum Creatinine = Micromol/Litre Constant = 1.23 For Men; 1.04 For Women

CKD-EPI equation

A general practice and public health perspective favours 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 × min(Scr/κ ,1)α × max(Scr/κ ,1)-1.209 × 0.993Age × 1.018 [if female] × 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.

Paediatric

Schwartz formula

$$\text{Creatinine clearance (ml/min)} = \frac{\text{constantb} \times \text{height (cm)}}{\text{serum creatinine (mg/dl)}}$$

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

	Serum creatinine		**Creatinine clearance**
Monitoring before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			<60 ml/min
First month after start of therapy or dose modification	Weekly	and	Weekly
Thereafter	Monthly	and	Monthly
Reduction of daily dose by 7 mg/kg/day, if following renal parameters are observed at two consecutive visits and cannot be attributed to other causes			
Adult patients	>33% above pre-treatment average	and	Decreases<LLN(90ml/min)
Paediatric patients	> age appropriate ULN	And/or	Decreases<LLN(90ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	And/or	Decreases<LLN(90ml/min)

LLN, lower limit of the normal range; ULN, upper limit of the normal range.

Treatment may be reinitiated depending on the individual clinical circumstances. Dose reduction or interruption may be also considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated:
• Proteinuria (test should be performed prior to therapy and monthly thereafter)
• Glycosuria in patients without diabetes and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

Renal tubulopathy has been mainly reported in children and adolescents with β-thalassaemia treated with deferasirox. Paediatric patients with thalassaemia may be at greater risk for renal tubulopathy (particularly metabolic acidosis)
Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:
• Serum creatinine remains significantly elevated and
• Persistent abnormality in another marker of renal function (eg, proteinuria, Fanconi syndrome). Consider hyperammonemic encephalopathy and early measurement of

ammonia levels if patients develop unexplained changes in mental status while on deferasirox therapy, particularly in children.

4.3 Liver function test elevations

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 pre-existing liver cirrhosis. However, the role of deferasirox as a contributing or aggravating factor cannot be excluded.

If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious reinitiation of treatment at a lower dose followed by gradual dose escalation may be considered.

Monitoring requirements for liver function tests

Monitor	**Frequency**
Serum transaminases Bilirubin Alkaline phosphatase	Serum transaminases, bilirubin and alkaline phosphatase should be checked prior to therapy, every 2 weeks during the first month and monthly thereafter

Consider hyperammonemic encephalopathy and early measurement of ammonia levels if patients develop unexplained changes in mental status while on deferasirox therapy, particularly in children.

4.4 Auditory (decreased hearing)

Auditory (decreased hearing) disturbances have been reported in patients treated with deferasirox, however they are uncommon. Auditory testing is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Monitoring	**Frequency**	**Action**
Auditory	Auditory monitoring recommended prior to therapy and yearly thereafter	If disturbances in hearing during treatment, consider dose reduction or interruption

4.5 Ocular disturbances (lens opacities)

Ocular disturbances (lens opacities) have been reported in patients treated with deferasirox, however they are uncommon.

Ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months).
If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Monitoring	**Frequency**	**Action**
Ophthalmic (including fundoscopy)	Ophthalmic monitoring recommended prior to therapy and yearly thereafter	If disturbances in vision during treatment, consider dose reduction or interruption

4.6 Over chelation in NTDT

Chelation therapy should only be initiated when there is evidence of iron overload (LIC ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of overchelation in all patients.

In paediatric patients with NTDT, dosing should not exceed 7 mg/kg/day. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every 3 months when serum ferritin is ≤800 µg/l.

Monitoring	Frequency	Action
Serum ferritin (SF)	Prior to therapy and monthly thereafter	If SF <300 µg/l, interrupt treatment
Liver iron concentration (LIC)	All patients: Prior to therapy Paediatric patients only: Every 3 months if SF is ≤800 µg/l	If SF <3 mg Fe/g dw, interrupt treatment

5. Other monitoring recommendations & actions

Please refer to table below for treatment interruption conditions.

Consideration	**Treatment interruption conditions**
SF	Consistently <500 µg/l (in transfusional iron overload) or < 300 µg/l (in NTDT syndromes)
Serum creatinine	Adult and paediatric: 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

Consideration	Treatment interruption conditions
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 transaminases (ALT and AST)	Persistent and progressive increase in liver enzyme levels
Metabolic acidosis	Development of metabolic acidosis
SJS, TEN, or any other severe skin reaction (eg, DRESS)	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 during the treatment (also consider dose reduction)
Unexplained cytopenia	Development of unexplained cytopenia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; DRESS, drug reaction with eosinophilia and systemic symptoms; LLN, lower limit of the normal range; NTDT, non–transfusion-dependent thalassaemia; SF, serum ferritin; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Please refer to the table below for appropriate monitoring and disease markers.

	Baseline	**In the first month after initiation of deferasirox or after dose modification**	**Monthly**	**Every 3 months**	**Yearly**
SF	√		√		
LIC	√			√ (for paediatric patients with NTDT only, if SF is ≤800 µg/l)	

	Baseline	**In the first month after initiation of deferasirox or after dose modification**	**Monthly**	**Every 3 months**	**Yearly**
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	√		√		
Body weight, height, and sexual development	√				√
Auditory/ophthalmic testing (including fundoscopy)	√				√

6. Reporting suspected adverse reactions

If you have a question about the product, If you want to report a adverse drug reaction, Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Alternatively adverse drug events may also be reported to rp@ejbusuttil.com**.**