Important Information for Healthcare Professionals to Remember About Deferasirox Accord (deferasirox) Treatment

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

See deferasirox SmPC for further details.

Approved by HPRA

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1. What is deferasirox?

Licensed indications[1]

Chronic Transfusional Iron Overload

Deferasirox Accord is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta-thalassaemia major aged 6 years and older.

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

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

Non–Transfusion-Dependent Thalassaemia (NTDT)

Deferasirox Accord 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 (NTDT) syndromes aged 10 years and older.

2. Formulation and method of administration

Deferasirox Accord is supplied as film-coated tablets which are available in three strengths[1] : 90 mg, 180mg, 360mg.

Different other deferasirox products might be available commercially, with different formulation apart from film-coated tablets (dispersable tablets, granules):

- To avoid errors, prescriptions must specify the type of formulation, the prescribed dose in mg/kg/day, and the calculated dose per day, with the strength of the chosen pharmaceutical form.
- The SmPC should be consulted for further info on the adequate posology and conditions of administration.

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

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

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[1]
- Doses >14 mg/kg/day are not recommended[1]
- Only one course of treatment with deferasirox is recommended for patients with NTDT[1]
- Monitor your patients' renal and hepatic function and serum ferritin levels regularly to ensure proper treatment[1]
- Chelation therapy should only be initiated when there is evidence of iron overload[1] (liver iron concentration [LIC] ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l)[1]
- Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients[1]

Deferasirox: Starting dose and dose adjustment for patients with NTDT[1]			
INITIATE deferasirox[a]	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[a]	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
LIC ≥5 mg Fe/g dw OR SF consistently >800 µg/l	LIC ≥7 mg Fe/g dw OR SF consistently >2000 µg/l	LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l	**GOAL** **LICb <3 mg Fe/g dw OR** **SF consistently <300 µg/l**

dw, dry weight; LIC, liver iron concentration; NTDT, non–transfusion-dependent thalassaemia; SF, serum ferritin.

[a] Doses above 14 mg/kg/day are not recommended for patients with NTDT. In paediatric patients with NTDT, dosing should not exceed 7 mg/kg. In patients in whom LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 7 mg/kg.

[b] LIC is the preferred method of iron overload determination.

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

Paediatric NTDT patients[1]

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[1]
- Doses >28 mg/kg/day are not recommended[1]
- Monitor your patients' renal and hepatic function and serum ferritin levels regularly to ensure proper treatment[1]
- Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients[1]

Deferasirox: Starting dose and dose adjustment for patients with transfusional iron overload[1]			
INITIATE deferasirox therapy	UP-TITRATE to achieve goal 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 <7 ml/kg/month of PRBCs (~ <2 units/month for an adult)	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 >14 ml/kg/month of PRBCs (~ >4 units/month for an adult)	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	

PRBCs, packed red blood cells; SF, serum ferritin; U, units.

* It is recommended that serum ferritin be monitored every month and that the dose of deferasirox be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin.

Paediatric transfusional iron overload patients1

- 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.[1]

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.[1]

Body weight, height and sexual development testing should be conducted annually in paediatric patients.[1]

4.2 Dose-dependent rise in serum creatinine

Monitoring serum creatinine and creatinine clearance (CrCl)[1]

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[1]

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[2]

The Cockcroft–Gault formula employs creatinine measurements and the patient's weight to predict CrCl.

The formula states CrCl in ml/min

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

AGE = YEARS
WEIGHT = IDEAL BODY WEIGHT IN KG
SERUM CREATININE = MICROMOL/LITRE
CONSTANT =
1.23 FOR MEN;
1.04 FOR WOMEN

CKD-EPI equation[3, 4]

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) = $141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [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[5]

$$\text{Creatinine clearance (ml/min)} = \frac{\text{constant}^{[a]} \times \text{height (cm)}}{\text{serum creatinine (mg/dl)}}$$

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

[a]The constant is 0.55 in children and adolescent girls, or 0.70 in adolescent boys.

The Modification of Diet and Renal Disease formula automatically estimates GFR based on body surface area, in units of ml/min/1.73 m2, considering age, gender and ethnicity.

Creatinine clearance = 32788 X creatinine –1.154 X age –0.203 X constant (ml/min/1.73m^2)

The constant in this equation is 1 for a white man, 0.742 for women, and must be again multiplied by 1.21 for black patients. The formula gives the creatinine value in µmol/l.

Renal monitoring and actions[1]

	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 (<90 ml/min)
Paediatric patients	>age appropriate ULN	and/ or	Decreases <LLN (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/ or	Decreases <LLN (<90 ml/min)

Adapted from reference 1

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. Deferasirox has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min.
- Persistent abnormality in another marker of renal function (eg, proteinuria, Fanconi syndrome).

4.3 Liver function test elevations[1]

Liver function test elevations have been observed in patients treated with deferasirox. Post- marketing 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.

It is not recommended to prescribe to patients with pre-existing severe hepatic diseases.

Monitoring requirements for liver function tests

Monitor	Frequency[1]
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**

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.

Interrupt treatment if persistent and progressive increase in serum transaminase levels is noted that cannot be attributed to other causes.

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

There have been post-marketing reports of metabolic acidosis occurring during treatment with deferasirox. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of deferasirox therapy should be considered in patients who develop metabolic acidosis.

4.4 Auditory (decreased hearing)[1]

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[1]	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)[1]

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[1]	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 Overchelation in NTDT[1]

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.[1]

Monitor	Frequency[1]	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 LIC <3 mg Fe/g dw, interrupt treatment

5. Treatment interruption and monitoring recommendation

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
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)	
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, height, and sexual development	✓				✓[b]
Auditory/ ophthalmic testing (including fundoscopy)	✓				✓

LIC, liver iron concentration; SF, serum ferritin.

[a] 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 minimise the risk of overchelation in all patients. Dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels are recommended during periods of treatment with high doses and serum ferritin values close to the target range, to avoid overchelation.

[b] Paediatric patients only.

The results of the tests for serum creatinine, CrCl, plasma cystatin C, proteinuria, serum ferritin, liver transaminases, bilirubin, and alkaline phosphatase should be recorded and regularly assessed for trends. The results should also be noted in the patient's charts, along with pre-treatment baseline levels for all tests.[1]

6. Reporting suspected adverse reactions

If you get side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the patient information leaflet.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Malta Medicines Authority ADR reporting form available online at http://medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Malta Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN or sent by email to: postlicensing.medicinesauthority@gov.mt

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