Important Information for Healthcare Professionals to Remember About Cipla Deferasirox Treatment

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

Please refer to the full product information available at https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=pi&q=deferasirox before prescribing this product.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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1. What is deferasirox?

Therapeutic indications[1]

The treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older.

The treatment of chronic iron overload in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine therapy or in whom desferrioxamine has proven ineffective.

The treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

Mechanism of action[1]

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 very 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 Cipla Deferasirox. It provides detailed information on dosage and required monitoring of patients being treated with Cipla Deferasirox, to minimise potential safety risks.

For further copies, please contact CIPLA on 03 9696 4438 or au.medinfo@cipla.com.

For full safety information, please refer to Cipla Deferasirox Product Information.

2. Formulation and method of administration

Cipla Deferasirox is supplied as a Film-coated tablet. This is available in three strengths:

90 mg: Light pink oval biconvex film-coated tablet, debossed with ‘C391’ on one side and plain on the other.

180 mg: Light pink oval biconvex film-coated tablet, debossed with ‘C392’ on one side and plain on the other.

360 mg: Light pink oval biconvex film-coated tablet, debossed with ‘C393’ on one side and plain on the other.

The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, Cipla Deferasirox 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.

Cipla Deferasirox 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. The film-coated tablets should not be taken with a high fat 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)

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 over-chelation.

- The recommended initial dose of Cipla deferasirox: 7 mg/kg body weight/day
- Doses above 14 mg/kg are not recommended
- It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimise the risk of over-chelation
- 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.

Table: NTDT: Recommended doses

	Deferasirox dispersible tablets	**Cipla 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 microgram/L
Adjustment steps (every 3-6 months)	Increase		≥7 mg Fe/g dw	or	>2,000 microgram/L
	5-10 mg/kg/day	3.5 - 7 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 microgram/L
	5-10 mg/kg/day	3.5 - 7 mg/kg/day			
Maximum dose	20 mg/kg/day	14 mg/kg/day			
	10 mg/kg/day	7 mg/kg/day	Not assessed	and	≤2,000 microgram/L
Dose Interruption			<3 mg Fe/g dw	or	<300 microgram/L
Re-initiation			if clinical evidence of chronic iron overload		

* LIC is the preferred method of determining iron overload

3.2 Dosing for patients with chronic transfusional iron overload

- Recommended initial dose of Cipla Deferasirox: 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.
- Patients not adequately controlled with doses of 21 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 28 mg/kg may be considered.
- Cipla Deferasirox film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the deferasirox dispersible tablet formulation.
- The dose of Cipla Deferasirox film-coated tablet should be 30% lower than the dose of deferasirox dispersible tablet, rounded to the nearest whole tablet.

Table: Transfusional iron overload: Recommended doses

	Deferasirox dispersible tablets	**Cipla Deferasirox film-coated tablets**	**Transfusions**	**Serum ferritin**
Starting dose	20 mg/kg/day	14 mg/kg/day	After 20 units or (about 100 mL/kg) of PRBC*	>1,000 micro-gram/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 desferrioxamine **	Half of desferrioxamine dose	One third of desferrioxamine dose		
Adjustment steps (every 3-6 months)	Increase			>2,500 micro-gram/L
	5-10 mg/kg/day Up to 40	3.5 - 7 mg/kg/day		

	Deferasirox dispersible tablets	Cipla Deferasirox film-coated tablets	Transfusions	Serum ferritin
	mg/kg/day	Up to 28 mg/kg/day		
	Decrease 5-10 mg/kg/day	3.5 - 7 mg/kg/day		
	When target is reached			500-1,000 microgram/L
Maximum dose	40 mg/kg/day	28 mg/kg/day		
Consider dose interruption				<500 micro-gram/L

* Packed Red Blood Cells
** For patients already well-managed on treatment with desferrioxamine

If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered.

Paediatric patients[1]

- The dosing recommendations for paediatric 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 minimise the risk of over-chelation.
- Changes in weight of paediatric patients over time must be taken into account when calculating the dose.
- As a general precautionary measure, body weight and longitudinal growth in paediatric patients can be monitored at regular intervals (every 12 months).
- In children aged between 2 and 5 years, exposure to deferasirox 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.

4. Safety and important monitoring requirements

4.1 Unknown consequences of long-term use in paediatric patients

For paediatric 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.

Body weight, height and sexual development should be monitored prior to therapy and at regular intervals (every 12 months). in paediatric patients.

4.2 Dose-dependent rise in serum creatinine

Monitoring serum creatinine and creatinine clearance (CrCl)

Acute renal failure, fatal in some patients and requiring dialysis in others, has been reported following the post-marketing use of deferasirox. Most fatalities occurred in patients with multiple co-morbidities and who were in advanced stages of their haematological disorders. It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy, to establish a reliable pre-treatment baseline and monitored monthly thereafter.

Deferasirox has not been studied in patients with renal impairment and must be used with caution in such patients. 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.

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 90 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. Reduce dose by 50 % in patients with renal impairment (CrCl 40 – 60 mL/min)

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.

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[2]

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

Estimated creatinine clearance in mL/minute

Males = (140-age) x weight (kg) / 0.814 x plasma creatinine (umol/L)

Females = 0.85 x (140-age) x weight (kg) / 0.814 x plasma creatinine (umol/L)

AGE in Years

CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[3,4]
A general practice and public health perspective favours adoption of the CKD-EPI equation in North America, Europe, and Australia for adults and using it as a comparator for new equations in all locations.
Glomerular filtration rate (GFR) = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [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[5]

$$\text{Creatinine clearance (mL/min)} = \frac{k \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

k The constant is 0.55 in children and adolescent girls, or 0.70 in adolescent boys.

Renal monitoring and actions[1]

	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 7 mg/kg/day (film-coated tablets) 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)		
Peadiatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and paediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		

* 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:
Tests for proteinuria should be performed monthly.

Renal tubulopathy has been reported in patients treated with deferasirox. The majority of these patients were children and adolescents with beta-thalassaemia and serum ferritin levels <1,500 microgram/L.

4.3 Liver function test elevations[1]

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 should not be used 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 were not influenced by such transaminase levels.

There have been post-marketing reports of hepatic failure in patients treated with deferasirox. Most reports of hepatic failure occurred in patients greater than 55 years of age and in patients with significant comorbidities including liver cirrhosis and multi-organ failure. Fatal outcomes were reported in some of these patients.

Monitoring requirements for liver function tests

Monitor	**Monitoring Frequency**
Serum transaminases Bilirubin and Alkaline phosphatase	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 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 treatment at a lower dose followed by gradual dose escalation may be considered.

4.4 Auditory (decreased hearing)[1]

Auditory (decreased hearing) disturbances have been reported with deferasirox treatment. Auditory testing is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months).
If disturbances are noted, 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)[1]

Ocular (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) disturbances have been reported with deferasirox treatment.

Monitoring	Frequency	Action
Ophthalmic testing (including slit lamp examination and dilated fundoscopy)	Before the start of deferasirox treatment and at regular intervals thereafter (every 12 months).	If disturbances are noted, dose reduction or interruption may be considered

4.6 Overchelation in NTDT[1]

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 over-chelation.

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.

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.

5. Other monitoring recommendations & actions[1,2]

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 >ULN.
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
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; ULN, Upper 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.

Consideration	Baseline	In the first month after initiation of Cipla Deferasirox or after dose modification	Monthly		Yearly
SF	✓				
LIC[a]	✓				
Serum Creatinine	2X	Weekly (Should also be tested weekly in the first month after	✓		

Consideration	**Baseline**	**In the first month after initiation of Cipla Deferasirox or after dose modification**	**Monthly**		**Yearly**
		dose modification)			
Creatinine clearance	✓	Weekly (Should also be tested weekly in the first month after dose modification)	✓		
Proteinuria	✓		✓		
Serum transaminases (ALT and AST)	✓	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.

b Paediatric patients only.

The results of the tests for serum creatinine, CrCl, 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.

6. Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

If you have a question about the product, please contact Cipla via email at drugsafety@Cipla.com or call at 1800-569-074

References:

1. Australian Product Information Cipla Deferasirox film coated tablets, Cipla.
2. Cockcroft DW, Gault MH. Nephron. 1976;16(1): 31–41.
3. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Ann Intern Med. 2012;156(11):785–795.
4. Levey AS, Stevens LA, Schmid CH, et al.; for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Ann Intern Med. 2009;150(9):604–612.
5. Schwartz GJ, Brion LP, Spitzer A. Pediatr Clin North Am. 1987;34(3):571–590.