Important Information to Remember About

IROREST (deferasirox)

Physician guide

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Welcome to your **IROREST** Handbook!

It has important information, including dosing for patients with chronic transfusional iron overload. Monitoring your patient treatment, safety profile and possible side effects.

Indications[1]

Chronic Transfusional Iron Overload

IROREST (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-thalassemia major aged 6 years and older.

IROREST 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 β-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 β-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

IROREST 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[1]

• IROREST is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients

• IROREST is contraindicated for use in combination with other iron chelator therapies as the safety of such combinations has not been established

• IROREST is contraindicated in patients with estimated CrCl <60 ml/min

- IROREST has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min.

Starting IROREST (deferasirox) treatment

Before initiating therapy

Pretreatment Measures1	
Test	**Pretreatment**
SF	✓
LICa	✓
Serum creatinine	**2×**
CrCl and/or plasma cystatin C	✓
Proteinuria	✓
Serum transaminase	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight, height, and sexual development (pediatric patients)	✓

CrCl, creatinine clearance; LIC, liver iron concentration; SF, serum ferritin.

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.

Dosing for patients with chronic transfusional iron overload

• Recommended initial dose: 14 mg/kg/day body weight[1]

• Doses >28 mg/kg/day are not recommended[1]

• Monitor your patients regularly to ensure proper treatment[1]

IROREST (deferasirox) starting dose and dose adjustment for patients with transfusional iron overload1			
INITIATE	**UP-TITRATE**	**DOWN-TITRATE**	**INTERRUPTION**
IROREST therapy	**to achieve Target SF when necessary**	**to avoid over chelation**	**Consider interruption once** **target SF has been achieved**
14 mg/kg body weight (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 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 <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 >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 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 IROREST (deferasirox) film-coated tablets that is numerically one third that of the deferoxamine dose could be considered	Increase in increments of 3.5 to 7 mg/kg/day if dose is <14 mg/kg body weight and sufficient efficacy is not obtained	Decrease dose in steps of 3.5 to 7 mg/kg when SF persistently <2500 µg/l and showing a decreasing trend over time, or closely monitor renal and hepatic function andserum ferritin levels	

PRBCs, packed red blood cells; U, units.

Pediatric transfusional iron overload patients1

• 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 minimise the risk of overchelation

• 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

Dosing for patients with non—transfusion dependent thalassemia (NTDT)

• Recommended initial dose: 7 mg/kg/day body weight[1]

• Doses >14 mg/kg/day are not recommended[1]

• Only one course of treatment with IROREST is recommended for patients with NTDT[1]

• Monitor your patients regularly to ensure proper treatment[1]

IROREST (deferasirox) starting dose and dose adjustment for patients with non—transfusion-dependent thalassemia1			
INITIATE	**UP-TITRATE**	**DOWN-TITRATE**	**STOP**
therapy	to achieve target SF when necessary	to avoid over chelation	therapy once target SF has been achieved
7 mg/kg/day	Increase in increments of 3.5 to 7 mg/kg/day	Decrease dose to 7 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.

[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 patients1

In pediatric patients, dosing should not exceed 7 mg/kg. LIC should be monitored every 3 months when SF is ≤800 µg/l in order to avoid overchelation.1

WARNING: Data in children with NTDT are very limited. As a consequence, IROREST therapy should be closely monitored to detect side effects and to follow iron burden in the pediatric population. In addition,

before administering IROREST 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

Considerations for treatment interruption of IROREST (deferasirox)[1]

Consideration	Treatment interruption conditions
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, 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 or any other severe skin reaction	Suspicion of reaction: discontinue immediately and do not reintroduce
Hypersensitivity reactions	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

LLN, lower limit of normal; SJS, Stevens-Johnson syndrome.

Monitoring recommendations for patients prior to and during IROREST (deferasirox) treatment[1]

	Baseline	In the first month after initiation of IROREST or after dose modification	Monthly	Every 3 months	Yearly
SF	✓		✓		
LICa	✓			✓ **(for pediatric patients only, if SF is ≤800 µg/l)**	
Serum creatinine	**2×**	**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 (pediatric patients)	✓				✓
Auditory/ophthalmic testing (including funduscopy)	✓				✓

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 charts, along with pretreatment baseline levels for all tests

Renal safety profile

Findings from clinical trials

Parameters measured in clinical trials1

In IROREST (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%.2 This is why duplicate serum creatinine values are recommended before initiating treatment with

IROREST. 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 studies1

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 CrCl1

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 IROREST, and monthly thereafter.**

Methods for estimating CrCl1

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

Adult

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

Cockcroft–Gault formula3 The Cockcroft-Gault formula employs creatinine measurements and the patient's weight to predict CrCl.
The formula states CrCl in ml/min

Creatinine Clearance=

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72^{a} \times \text{serum creatinine (mg/100 ml)}}$$

In female patients, creatinine clearance is multiplied by 0.85.

CKD-EPI equation4,5 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 × 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.

Pediatric

Schwartz formula[6]

Creatinine clearance (ml/min) =

$$\frac{\text{Constant}^{b} \times \text{hight (cm)}}{\text{serum creatinine (mg/dl)}}$$

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 safety profile (continued)

Renal monitoring and actions

Reduce the dose by 7 mg/kg, if serum creatinine rises.

- **Adult:** >33% above baseline and CrCl <LLN (90 ml/min) at two consecutive visits.
- **Pediatric:** either > age – appropriate ULN or CrCl falls to <LLN (<90 ml/min) at two consecutive visits.

Interrupt treatment after dose reduction if
• Serum creatinine remains >33% above baseline, and/or
• CrCl <LLN (<90 ml/min)
• Treatment may be reinitiated depending on the individual clinical circumstances

If clinically indicated, monitor **renal tubular function** (eg, proteinuria, glycosuria in patients without diabetes and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)
• Consider dose reduction or interruption if there are abnormalities
• Renal tubulopathy has been mainly reported in children and adolescents with β-thalassemia treated with IROREST.

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.

Hepatic safety profile

Liver function assessment
Liver function test elevations have been observed in patients treated with IROREST (deferasirox)
• Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with IROREST.
• Most reports of hepatic failure involved patients with significant morbidities including preexisting liver cirrhosis.
• However, the role of IROREST as a contributing or aggravating factor cannot be excluded.

Monitor **liver function** prior to prescription, then at monthly intervals or more often if clinically indicated
• Interrupt treatment if persistent and progressive increase in liver enzyme is noted.

Recommendations in hepatic impairment:

Exjada 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 IROREST 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.

Please refer to the summary of product characteristics for more information.

You can report any problem or adverse events through:

Apotex Saudi contact information:

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Mobile: +966 55 111 9619
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Website: https://ade.sfda.gov.sa/

By reporting side affects you can help provide more information on the safety of this medicine.

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References

IROREST SPC.