

Important Information to Remember About Deferasirox Treatment

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

This document has been reviewed and approved by The Saudi Food and Drug Authority (SFDA).

Indications¹

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.

Contraindications¹

- 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 ¹	
Test	Pretreatment
SF	✓
LIC ^a	✓
Serum creatinine	2x
CrCl and/or plasma cystatin C	✓
Proteinuria	✓
Serum transaminases (ALT and AST)	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight and height	✓
Sexual development (pediatric patients)	✓

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

^aFor 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.¹

Switch between EXJADE film-coated tablets/granules and generic version of deferasirox dispersible tablets

In the KSA, medicines containing deferasirox are available as film-coated tablets as film-coated tablets in dose strengths of 90 mg, 180 mg, and 360 mg and as dispersible tablets in dose strengths of 125 mg, 250 mg, and 500 mg marketed under different tradenames as generic alternatives to EXJADE. Due to a different pharmacokinetic profile established between EXJADE film-coated tablets and EXJADE dispersible tablets, 30% smaller dose of the film-coated tablets is needed in comparison to the recommended dose for the dispersible tablets

As a reference, the corresponding doses for Exjade FCT/granules and Exjade DT are shown in the tables below.

Transfusional iron overload:

	Exjade film-coated tablets/granules	Exjade Dispersible tablets
Starting dose	14 mg/kg/day	20 mg/kg/day
Alternative starting doses	7 mg/kg/day 21 mg/kg/day	10 mg/kg/day 30 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day
Maximum dose	28 mg/kg/day	40 mg/kg/day

NTDT syndromes:

	Exjade film-coated tablets/granules	Exjade Dispersible tablets
Starting dose	7 mg/kg/day	10 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day
Maximum dose	14 mg/kg/day	20 mg/kg/day

Important differences between Exjade film-coated tablets and granules

Exjade film-coated tablets¹

Strengths:
90 mg
180 mg
360 mg
(oval, blue
tablets)

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, Exjade film-coated tablets may be crushed and administered by sprinkling onto soft food (eg, yogurt or applesauce)

Does not contain lactose

 90 mg

 180 mg

 360 mg

[insert photograph of local packaging for Exjade film-coated tablets]

Exjade granules¹

Strengths:
90 mg
180 mg
360 mg
(white to almost-white
granules in
sachet)

May be taken on an empty stomach or with a light meal

Granules should be administered by sprinkling onto food (eg, yogurt or applesauce)

Does not contain lactose

125 mg



250 mg



500 mg



Tablets and granules displayed are not actual size.

Exjade® film-coated tablets/granules dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 14mg/kg/day body weight¹
- Doses >28 mg/kg/day are not recommended¹
- Monitor your patients regularly¹

Exjade (deferasirox) film-coated tablets/granules starting dose and dose adjustment for patients with transfusional iron overload¹

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 closely monitor renal and hepatic function and serum ferritin levels	
7 mg/kg body weight per day <7 ml/kg/month of PRBCs (~<2units/monthforanadult)	Increase in increments of 3.5 to 7 mg/kg/day up to maximum dose of 28mg/kg/day	—————	
21 mg/kg body weight per day >14 ml/kg/month of PRBCs (~>4 units/monthfor anadult)	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, closely monitor renal and hepatic function and serum ferritin levels.	SF consistently <500 µg/l
Patients already well managed on treatment with deferoxamine A starting dose of Exjade 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 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, closely monitor renal and hepatic function and serum ferritin levels	

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

^aIn addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

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

Exjade® film-coated tablets/granules dosing for patients with non–transfusion-dependent thalassemia (NTDT)

- Recommended initial dose: 7 mg/kg/day body weight^{1,2}
- Doses >14 mg/kg/day are not recommended¹
- Only one course of treatment with Exjade is recommended for patients with NTDT¹
- Monitor your patients regularly¹

Exjade (deferasirox) film-coated tablets/granules starting dose and dose adjustment for patients with non—transfusion-dependent thalassemia¹

INITIATE therapy ^a	UP-TITRATE to achieve target SF when necessary ^{a,b}	DOWN-TITRATE to avoid overchelation	STOP therapy once target SF 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, 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 \geq 5 mg Fe/g dw OR SF consistently $>$ 800 μ g/l	LIC \geq 7 mg Fe/g dw OR SF consistently $>$ 2000 μ g/l	LIC $<$ 7 mg Fe/g dw OR SF consistently \leq 2000 μ g/l	GOAL LIC $<$ 3 mg Fe/g dw OR SF consistently $<$ 300 μ g/l

dw, dry weight; LIC, liver iron concentration; SF, serum ferritin.

^aDoses above 14mg/kg/day are not recommended for patients with NTDT. In patients in whom LIC was not assessed and SF is \leq 2000 μ g/l, dosing should not exceed 7 mg/kg/day.

^bIn 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/day. LIC should be monitored every 3 months when SF is \leq 800 μ g/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.

Considerations for treatment interruption or discontinuation of deferasirox¹

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		Persistent abnormalities in levels of tubular markers and/or if clinically indicated—also refer patient to renal specialist and consider biopsy in case of persistent abnormalities
Serum transaminase (ALT and AST)		Persistent and progressive increase in liver enzyme that cannot be attributed to other causes
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 treatment¹

	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	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 and height	✓				✓ in pediatric patients
Auditory/ophthalmic testing (including funduscopy)	✓				✓
Sexual development (pediatric patients)	✓				✓

^aFor 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 tests.

Renal safety profile

Findings from clinical trials

Parameters measured in clinical trials¹

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%.¹ 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 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 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.¹

Adult

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

Cockcroft–Gault

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

The formula states CrCl in ml/min.

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

In female patients, creatinine clearance is multiplied by 0.85.

CKD-EPI equation^{3,4}

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) = $141 \times \min(\text{Scr}/k, 1)^\alpha \times \max(\text{Scr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.4 for males, min indicates the minimum of Scr/ k or 1, and max indicates the maximum of Scr/ k or 1.

Pediatric

*Schwartz formula*⁵

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

Scr to be measured by Jaffe method.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

^aIf serum creatinine is provided in mmol/l instead of mg/dl, the constant should be 815 instead of 72.

^bThe constant is 0.55 in children and adolescent girls, or 0.70 in adolescent boys.

Renal safety profile(continued)

Renal monitoring and actions¹

Exjade® (deferasirox) film-coated tablets/granules: Reduce the dose by 7 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 abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated
- 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 assessment¹

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.

Liver function assessment¹

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.



**This medical product is subject to additional monitoring.
This will allow quick identification of new safety information.
Healthcare professionals are asked to report any suspected
adverse reactions via the national reporting system.**

References: 1. EXJADE® [KSA Summary of Product Characteristics (Dec 2022)
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):571-59

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