Novartis Oncology

Important Information to Remember About Exjade® (Deferasirox) Treatment

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EXJ HCP1 11/22 MT-FA-11557177

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.

Indications[1]

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.

Contraindications[1]

- 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.

[a]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.[1]

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

In the EU, medicines containing deferasirox are registered as film-coated tablets/granules 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, a 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 and Exjade DT are shown in the tables below.

Transfusional iron overload

	Exjade film-coated tablets	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	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

Exjade film-coated tablets[1]

Strengths: 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 (e.g., yogurt or applesauce).	Does not contain lactose  180 mg   360 mg 

Tablets displayed are not actual size.

Exjade film-coated tablets 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[1]

Exjade (deferasirox) film-coated tablets starting dose and dose adjustment for patients with transfusional iron overload[1]

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

Pediatric transfusional iron overload patients[1]

- 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 minimize 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

EXJ HCP1 11/22 MT-FA-11557177

Exjade® film-coated tablets 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 Exjade is recommended for patients with NTDT[1]
- Monitor your patients regularly[1]

Exjade (deferasirox) film-coated tablets starting dose and dose adjustment for patients with non—transfusion-dependent thalassemia[1]

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	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 ≥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** LIC <3 mg Fe/g dw OR SF consistently <300 µg/l

dw, dry weight; LIC, liver iron concentration; SF, serum ferritin.
[a]Doses above 14 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 7 mg/kg/day.
[b]In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric NTDT patients[1]

In pediatric 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 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 deferasirox[1]

Consideration	Conditions for treatment interruption
SF	Consider treatment interruption if SF consistently <500 µg/l (in transfusional iron overload) or <300 µg/l (in NTDT syndromes). Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.
Serum creatinine/ Creatinine clearance	Interrupt treatment in adult and pediatric patients: when serum creatinine remains >33% above baseline (pre-treatment average) and/or CrCl <LLN (90 ml/min) after dose reduction. Treatment may be reinitiated depending on the individual clinical circumstances. — also refer the patient to a renal specialist and consider biopsy
Proteinuria	Consider treatment interruption or dose reduction — also refer the patient to a renal specialist and consider biopsy in case of persistent abnormality
Tubular markers	Consider treatment interruption or dose reduction if there are abnormalities in levels of tubular markers and/or if clinically indicated — also refer the patient to a renal specialist and consider biopsy in case of persistent abnormalities
Serum transaminase (ALT and AST)	Treatment should be interrupted if there is a persistent and progressive increase in liver enzymes that cannot be attributed to other causes. Treatment can be cautiously re-initiated at a lower dose once liver function has returned to normal or the cause of the liver function test abnormalities has been clarified.
Metabolic acidosis	Consider treatment interruption with development of metabolic acidosis
Vision and hearing	Consider treatment interruption or dose reduction if there are disturbances of vision or hearing
Unexplained cytopenia	Consider treatment interruption with the development of unexplained cytopenia
Consideration	**Conditions for treatment discontinuation**
SJS, TEN, DRESS, or any other SCAR	Suspicion of any Severe Cutaneous Adverse Reaction (SCAR): discontinue treatment immediately and do not reintroduce
Hypersensitivity reactions (eg, anaphylaxis, angioedema)	Occurrence of reaction: discontinue treatment and institute appropriate medical intervention. Do not reintroduce in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock

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 treatment[1]

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

[a]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.

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.

EXJ HCP1 11/22 MT-FA-11557177

Renal safety profile

Findings from clinical trials

Parameters measured in clinical trials[1]

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 studies[1]

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 CrCl[1]

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 formula[2]

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 × min(Scr/κ ,1)$^{\alpha}$ × max(Scr/κ ,1)$^{-1.209}$ × 0.993^{Age} × 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 −0.41 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ 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.
[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[1]

Exjade (deferasirox) film-coated tablets: 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 ß-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 (e.g., 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 assessment[1]

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 that cannot be attributed to other causes

Recommendations in hepatic impairment[1]

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

Suspected Adverse Drug Reactions (side effects) and medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at

http://www.medicinesauthority.gov.mt/adrportal

and sent by post or email to;

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann. SGN 3000.

E: postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events associated with the use of EXJADE to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, online on www.report.novartis.com or by e-mail at drug_safety.malta@novartis.com.

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For electronic copies of this Educational Material, please refer to the Malta Medicines Authority website - http://www.medicinesauthority.gov.mt/rmm - and download the required material with the latest date.

REFERENCES

1. EXJADE® [EU Summary of Product Characteristics (25-Aug-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):571-590.

EXJ HCP1 11/22 MT-FA-11557177

For more detailed guidance on EXJADE please refer to the Summary of Product Characteristics (SmPC) available at:

https://www.ema.europa.eu/en/documents/product-information/exjade-epar-product-information_en.pdf

This educational material is a part of the conditions of the Marketing Authorisation

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EXJ HCP1 11/22 MT-FA-11557177