Novartis
Oncology

Important Information to Remember About Exjade®▼ (deferasirox) Treatment

▼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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. Adverse events should also be reported to Novartis Ireland by calling 01-2080612 or by email to drugsafety.dublin@novartis.com. If you use email please write "reporting of adverse event" in the mail heading.

NOVARTIS

HPRA approved March 2023 February 2023 | IE268641 v20.1

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 β-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 paediatric 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 paediatric and adult 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 paediatric and adult 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	×2
CrCl and/or plasma cystatin C	✓
Proteinuria	✓
Serum transaminases	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight and height	✓
Sexual development (paediatric 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 available 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 profiles, a 30% lower dose of Exjade® film-coated tablets is needed in comparison to the recommended dose for Exjade® dispersible tablets (see section 5.1 of SmPC). If a dispersible tablet formulation of deferasirox is available in your jurisdiction please ensure to apply the required dose adjustments when switching a patient from one formulation to the other.

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

- Recommended initial dose: 14 mg/kg/day body weight
- Doses >28 mg/kg/day are not recommended[1]
- Closely monitor your patient's renal and hepatic function and serum ferritin levels (refer to page 7 for further details)
- Caution should be taken during chelation therapy to minimise the risk of overchelation in all patients

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

Initiate therapy	**Up-Titrate** to achieve target when necessary[a]	**Down-Titrate** to avoid overchelation	**Interruption** Consider interruption once target 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 dose of 28 mg/kg/day**	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF=500-1000 µg/l, and to minimise overchelation risky, 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 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 dose of 28 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, or 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.

** In patients not adequately controlled with doses of 21 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/l and not showing a decreasing trend over time), doses of up to 28mg/kg may be considered. The availability of long-term efficacy and safety data with Exjade® dispersible tablets used at doses above 30mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation).

Paediatric transfusional iron overload patients[1]

- 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 (refer to page 7 for further details)

Exjade® film-coated tablets dosing for patients with non–transfusion-dependent thalassemia (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 µg/l)
- 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]
- Closely monitor your patient's renal and hepatic function and serum ferritin levels (refer to page 7 for further details)
- Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients

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 when necessary[ab]	DOWN-TITRATE to avoid overchelation	STOP therapy once target 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	Decrease dose to 7 mg/kg/day or less	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.

Paediatric NTDT patients[1]

In paediatric patients, 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 three months when ferritin is ≤800 µg/l.[1]

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. 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] A single course of treatment is proposed for NTDT patients.

Considerations for treatment interruption of deferasirox[1]

Consideration	Treatment interruption conditions
SF	Consistently <500 µg/l (in transfusional iron overload) or <300 µg/l or LIC <3 mg Fe/g dw (in NTDT syndromes)
Serum creatinine	Adult and paediatric: after dose reduction, remains >33% above pre-treatment average 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 (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	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

DRESS, drug reaction with eosinophilia and systemic symptoms; LLN, lower limit of normal; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

* 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 and
- Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi Syndrome).

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

	Base-line	In the first month after initiation of deferasirox or after dose modification	Monthly	Every 3 months	Yearly
SF	✓		✓		
LIC[a]	✓			✓ (for paediatric patients with NTDT 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 paediatric patients)
Sexual development (paediatric patients)	✓				✓
Auditory/ ophthalmic testing (including funduscopy)	✓				✓

[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]

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.

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.

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

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

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[1]

- Adult: serum creatinine >33% above baseline and CrCl <LLN (90 ml/min) at two consecutive visits and cannot be attributed to other causes
- Paediatric: 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

Adults and Paediatrics: Interrupt treatment after dose reduction if

- Serum creatinine remains >33% above baseline, and/or CrCl <LLN (<90 ml/min)

Consider dose reduction or interruption 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 non-diabetics 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-thalassemia treated with deferasirox

Refer patient to a renal specialist and consider further specialised investigations **(such as renal biopsy)** if the following occur despite dose reduction and interruption:

- Serum creatinine remains significantly elevated and persistent abnormality has been detected in another marker of renal function (eg, proteinuria, signs of Fanconi syndrome)

Particular attention should be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function, and in patients who are receiving high doses of deferasirox and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult).

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 diarrhoea or vomiting.

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.

Post-marketing cases of severe forms of renal tubulopathy (such as Fanconi syndrome) and renal failure associated with changes in consciousness in the context of hyperammonaemic encephalopathy have been reported in patients treated with deferasirox. Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox. Consider hyperammonemic encephalopathy and early measurement of ammonia levels if patients develop unexplained changes in mental status while on deferasirox therapy.

Hepatic safety profile

Liver function assessment

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. Severe forms associated with changes in consciousness in the context of hyperammonaemic encephalopathy, may occur in patients treated with deferasirox, particularly in children.

Consider hyperammonaemic encephalopathy and measure ammonia levels in patients who develop unexplained changes in mental status while on Exjade® therapy.

- 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

Check 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
- Consider cautious re-initiation of treatment at a lower dose followed by gradual dose escalation, once cause of liver function test abnormalities has been clarified or after return to normal levels'

Recommendations in hepatic impairment

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.

▼ This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions of the medicinal product is important to Novartis and the HPRA. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions along with the batch ID should be reported via HPRA Pharmacovigilance on www.hpra.ie. Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.

Please Note: Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Adverse events should also be reported to Novartis Ireland by calling 01-2080612 or by email to drugsafety.dublin@novartis.com.

Exjade® FCT (Film Coated Tablet) is the only formulation of this medication marketed in Ireland.

REFERENCES

1. Exjade® (deferasirox) film-coated tablets: EU Summary of Product Characteristics. Novartis; July 2019. **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.

NOVARTIS

Novartis Ireland Limited
Vista Building, Elm Park Business Park,
Merrion Road, Dublin 4, D04 A9N6

HPRA approved March 2023 February 2023 | IE268641 v20.1