Important Information to Remember About Deferasirox▼ Treatment

EXJ HCP 04/18 MT

April 2018

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[1,2]

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 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 pediatric 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 pediatric 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[1,2]

- 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[1,2]	
Test	**Pretreatment**
SF	✓
LIC[a]	✓
Serum creatinine	2×
CrCl and/or plasma cystatin C	✓
Proteinuria	✓
Serum transaminases (ALT and AST)	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight, height, and 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.[2]

Dose comparisons between Exjade® film-coated tablets and dispersible tablets

There are two formulations of deferasirox: Exjade film-coated tablets and Exjade dispersible tablets, each available in three strengths

- Film-coated tablets: 90 mg, 180 mg, and 360 mg
- Dispersible tablets: 125 mg, 250 mg, and 500 mg

Both formulations have the same active ingredient (deferasirox).

- Exjade film-coated tablets are a strength-adjusted formulation of deferasirox, with higher bioavailability than the dispersible tablets
- Both formulations are differentiated by tablet form, color, size, and packaging

A different posology and method of administration must be applied when switching patients from dispersible tablets to film-coated tablets of deferasirox.

Important differences between Exjade film-coated tablets and dispersible tablets

Exjade film-coated tablets	Exjade dispersible tablets
Strengths: 90 mg, 180 mg, 360 mg (oval, blue tablets)	Strengths: 125 mg, 250 mg, 500 mg (round, white tablets)
May be taken on an empty stomach or with a light meal	Must be taken on an empty stomach, at least 30 minutes before food
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)	Disperse tablets in water, orange juice, or apple juice. Dispersible tablets must not be chewed or swallowed whole
Does not contain lactose	Contains lactose
 90 mg	 125 mg
 180 mg	 250 mg
 360 mg	 500 mg

Tablets displayed are not actual size.

Converting from dispersible tablets to film-coated tablets

- The dose of the film-coated tablets should be 30% lower than the dose of dispersible tablets, rounded to the nearest whole film-coated tablet

To avoid dosing errors, it is important that the prescription specify both the type of formulation (dispersible tablet or film-coated tablet) and the calculated dose per day with strength of film-coated or dispersible tablets.

With the availability of a film-coated tablet formulation of deferasirox, dispersible tablets will no longer be available in the European Union in the near future.

Dose comparisons between Exjade film-coated tablets and dispersible tablets

Exjade film-coated tablets	Exjade dispersible tablets
Dose range: 7-28 mg/kg/day; calculated and rounded to the nearest whole tablet size	Dose range: 10-40 mg/kg/day; calculated and rounded to the nearest whole tablet size
Dose adjustment: increments of 3.5-7 mg/kg/day	Dose adjustment: increments of 5-10 mg/kg/day
Therapeutic dose range: 7 mg/kg/day 14 mg/kg/day (maximum recommended dose for NTDT patients) 21 mg/kg/day 28 mg/kg/day (maximum recommended dose for transfusional iron overload patients)	Therapeutic dose range: 10 mg/kg/day 20 mg/kg/day (maximum recommended dose for NTDT patients) 30 mg/kg/day 40 mg/kg/day (maximum recommended dose for transfusional iron overload patients)
Calculated daily dose example for 50 kg patient with transfusional iron overload receiving 21 mg/kg/day: 21 mg/kg/day × 50 kg = 1050 mg/day Three (3) 360 mg tablets	Calculated daily dose example for 50 kg patient with transfusional iron overload receiving 30 mg/kg/day: 30 mg/kg/day × 50 kg = 1500 mg/day Three (3) 500 mg tablets

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 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	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	
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	

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. 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 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 when necessary[a,b]	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.

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.[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 pediatric 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]

Exjade® dispersible tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 20 mg/kg/day body weight[2]
- Doses >40 mg/kg/day are not recommended[2]
- Monitor your patients regularly[2]

Exjade (deferasirox) dispersible tablets starting dose and dose adjustment for patients with transfusional iron overload[2]

INITIATE therapy	UP-TITRATE to achieve target when necessary[a]	DOWN-TITRATE to avoid overchelation	INTERRUPTION Consider interruption once target has been achieved
20 mg/kg body weight per day (recommended starting dose) 20 U (~100 ml/kg) PRBCs or SF >1000 µg/l	Increase in increments of 5 to 10 mg/kg/day up to a dose of 40 mg/kg/day	Decrease dose in steps of 5 to 10 mg/kg/day when SF=500-1000 µg/l	SF consistently <500 µg/l
10 mg/kg body weight per day <7 ml/kg/month of PRBCs (~ <2 units/month for an adult)	Increase in increments of 5 to 10 mg/kg/day up to a dose of 40 mg/kg/day	—	
30 mg/kg body weight per day >14 ml/kg/month of PRBCs (~ >4 units/month for an adult)	Increase in increments of 5 to 10 mg/kg/day up to a dose of 40 mg/kg/day	Decrease dose in steps of 5 to 10 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time	
Patients already well managed on treatment with deferoxamine Starting dose of Exjade dispersible tablets that is numerically half that of the deferoxamine dose	Increase in increments of 5 to 10 mg/kg/day if dose is <20 mg/kg body weight per day and sufficient efficacy is not obtained	Decrease dose in steps of 5 to 10 mg/kg/day when SF persistently <2500 µg/l and showing a decreasing trend over time	

PRBCs, packed red blood cells; 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[2]

- The dosing recommendations for pediatric patients aged 2 to 17 years with transfusional iron overload are the same as for adult patients. 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® dispersible tablets dosing for patients with non–transfusion-dependent thalassemia (NTDT)

- Recommended initial dose: 10 mg/kg/day body weight[2]
- Doses >20 mg/kg/day are not recommended[2]
- Only one course of treatment with Exjade is recommended for patients with NTDT[2]
- Monitor your patients regularly to ensure proper treatment[2]

Exjade (deferasirox) dispersible tablets starting dose and dose adjustment for patients with non–transfusion-dependent thalassemia[2]

INITIATE therapy[a]	UP-TITRATE to achieve target when necessary[a,b]	DOWN-TITRATE to avoid overchelation	STOP therapy once target has been achieved
10 mg/kg/day	Increase in increments of 5 to 10 mg/kg/day up to a maximum dose of 20 mg/kg/day for adult patients and 10 mg/kg/day for pediatric patients	Decrease dose to 10 mg/kg/day or less	Retreatment is not recommended for patients with NTDT
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.

[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/day.

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

Pediatric NTDT patients[2]

In pediatric patients, dosing should not exceed 10 mg/kg/day. LIC should be monitored every 3 months when SF is ≤800 µg/l in order to avoid overchelation.[2]

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. 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.[2]

Considerations for treatment interruption of deferasirox[1,2]

Consideration	Treatment interruption conditions
SF	Consistently <500 µg/l (in transfusional iron overload) or <300 µg/l (in NTDT syndromes)
Serum creatinine	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 (ALT and AST)	Persistent and progressive increase in liver enzyme
Metabolic acidosis	Development of metabolic acidosis
SJS, TEN, or any other severe skin reaction (eg, DRESS)	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

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

Monitoring recommendations for patients prior to and during deferasirox treatment[1,2]

	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, height, and sexual development (pediatric 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.[2]

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 trials[1,2]

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[1,2]

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[1,2]

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[1,2]

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[3]

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[4,5]

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) = $141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}}$ $\times 1.018$ [if female] $\times 1.159$ [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]

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

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[1,2]

Exjade® (deferasirox) film-coated tablets: Reduce the dose by 7 mg/kg/day, if[1]
Exjade® (deferasirox) dispersible tablets: Reduce the dose by 10 mg/kg/day, if[2]

- Adult: serum creatinine >33% above baseline and CrCl <LLN (90 ml/min) at two consecutive visits
- Pediatric: serum creatinine either above age-appropriate ULN and/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)

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 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.

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
- 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 **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

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.

EXJADE® film-coated tablets

▼ This medicinal 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. See section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION: film-coated tablets containing 180mg or 360mg deferasirox.

INDICATIONS: Treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. 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 beta thalassaemia 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 paediatric patients with beta thalassaemia 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 paediatric patients with other anaemias aged 2 years and older. Treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependant thalassaemia syndromes aged 10 years and older.

DOSAGE AND ADMINISTRATION: Transfusional iron overload ♦ Starting daily dose after transfusion of 20units of packed red blood cells (PRBC)**:** Recommended initial daily dose is 20 mg/kg body weight; consider 30 mg/kg for patients receiving >14 ml/kg/month of PRBC (>4 units/month for adults), and for whom the objective is reduction of iron overload; consider 10 mg/kg for patients receiving <7 ml/kg/month of PRBC (<2 units/month for adults), and for whom the objective is maintenance of the body iron level**;** for patients already well-managed on treatment with deferoxamine, consider a starting dose of EXJADE® that is numerically half that of the deferoxamine dose. ♦ Monthly monitoring of serum ferritin for assessing patient's response to therapy ♦ **Dose adjustment:** to be adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 to 10 mg/kg. In patients not adequately controlled with doses of 30 mg/kg, doses of up to 40 mg/kg may be considered. In patients whose serum ferritin level has reached the target (usually between 500 and 1000 microgram/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. EXJADE® should be interrupted if serum ferritin falls consistently below 500 micrograms/l. ♦ **Maximum daily dose** is 40 mg/kg body weight. **Paediatric patients:** aged 2-17years dosing is the same as for adults. However change in weight of patients must be taken into account when calculating the dose. **Non-transfusion-dependent thalassaemia syndromes.** 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). 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 over-chelation in all patients. ♦ **Starting daily dose:** The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight. ♦ **Dose adjustment:** It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes. In patients in whom LIC was not assessed and serum ferritin is ≤2,000 µg/l, dosing should not exceed 10 mg/kg. For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 µg/l. ♦ **Treatment cessation:** Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/l), treatment should be stopped. 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. ♦ **Paediatric patients:** In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. 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 serum ferritin is ≤800 µg/l. Before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known. ♦ EXJADE® must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. ♦ EXJADE® tablets to be dispersed in water or apple or orange juice. Any residue is to be re-suspended in water or juice and swallowed. Tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion respectively. ♦ EXJADE is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS: ♦Hypersensitivity to deferasirox or to any of the excipients. ♦Creatinine clearance <60 ml/min or serum creatinine >2 times the age-appropriate upper limit of normal. ♦Combination with other iron chelator therapies.

WARNINGS/PRECAUTIONS: ♦ This medicinal product is subject to additional monitoring. ♦*Renal function:* Deferasirox has been studied only in patients with baseline serum creatinine within the age-appropriate normal range. It is recommended that serum creatinine be assessed in duplicate before initiating therapy. Creatinine clearance, serum creatinine and/or plasma cystatin C levels should be monitored prior to therapy, weekly in first month after initiation or modification of therapy with EXJADE® and monthly thereafter. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting. Due to chances of metabolic acidiosis, in patients where acid-base imbalance is a known complication like diarrhea, renal impairment or renal tubulopathy (Fanconi's syndrome), acid-base balance should be monitored. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis. Dose reduction or interruption may also considered 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 beta-thalassaemia treated with EXJADE. Patients should be referred to a renal specialist, and further specialised investigations may be considered if serum creatinine remains significantly elevated and persistent abnormality in another marker of renal function. ♦ *Hepatic function:* Postmarketing cases of hepatic failure have been reported. Monitoring of serum transaminases, bilirubin and alkaline phosphatase: before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. EXJADE® should be interrupted if persistent and progressive unattributable increase in serum transaminases levels. Not recommended in patients with severe hepatic impairment. ♦ *Gastrointestinal:* Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. There have been rare reports of fatal GI haemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 x 10^9/L. ♦*Skin disorders:* EXJADE® should be interrupted if any severe cutaneous adverse reactions develop. Patients should be advised of signs and symptoms of severe skin reaction, and be closely monitored. ♦*Blood disorders:* There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with EXJADE. ♦ Caution in elderly patients due to a higher frequency of adverse reactions. ♦ Monthly monitoring of serum ferritin is recommended to assess patient's response to therapy. ♦ Not recommended in patients with short life expectancy (e.g. high risk myelodysplastic syndrome) especially when co-morbidities could increase the risk of adverse events. ♦ Monitor cardiac function in patients with severe iron overload during long term treatment with EXJADE®. ♦ As a general precaution, in paediatric patients with transfusional iron overload, monitor body weight, height and sexual development. ♦*Hypersensitivity reactions:* Discontinue if severe hypersensitivity reaction occurs. ♦*Vision and hearing:* Recommended ophthalmological/audiological testing before start of treatment and annually. ♦ In patients who develop unexplained cytopenia consider interruption of treatment. ♦ Should not be used during pregnancy unless clearly necessary.♦ Not recommended when breast-feeding. ♦ Caution when driving or operating machinery.♦ Product contains lactose. ♦ Exjade may decrease the efficacy of hormonal contraceptives. Women of childbearing potential are recommended to use additional or alternative non hormonal methods of contraception when using EXJADE.

INTERACTIONS: ♦ Should not be taken with aluminium-containing antacids or with other iron chelator therapies. ♦Caution when combined with drugs metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, bepridil, ergotamine, hormonal contraceptive agents). ♦ The concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.♦Concomitant use with repaglinide should be avoided. If combination is necessary, careful monitoring of glucose levels should be performed. An interaction between EXJADE® and other CYP2C8 substrates like paclitaxel cannot be excluded. ♦ The concomitant administration of deferasirox with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity. ♦An interaction between deferasirox and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline. ♦The concomitant administration of deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

ADVERSE REACTIONS: ♦ **Very common**: blood creatinine increased ♦ **Common:** headache, proteinuria, transaminases increased, rash, pruritus, diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia ♦ **Uncommon:** anxiety, sleep disorder, dizziness, cataract, maculopathy, deafness, laryngeal pain, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, pyrexia, oedema, fatigue, renal tubular disorder (acquired Fanconi's syndrome), glycosuria ♦ **Rare:** oesophagitis, optic neuritis ♦ Not known: metabolic acidosis, neutropenia, gastrointestinal perforation, acute pancreatitis, nephrolithiasis, renal tubular necrosis**,** anaemia aggravated,pancytopenia, thrombocytopenia, hypersensitivity reactions (including anaphylactic reactions and angioedema), acute renal failure, Stevens-Johnson syndrome, leukocytoclastic vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis, hepatic failure, tubulointerstitial nephritis

LEGAL CATEGORY: POM

PACK SIZES: Packs of 30 film-coated tablets

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR, United Kingdom.

MARKETING AUHORISATION NUMBER: EU/1/06/356/014 and 017

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872

2017-MT-EXJ-14-AUG-2017

References: 1. Data on file. Novartis Pharmaceuticals Corp. **2.** Exjade® (deferasirox) dispersible tablets: EU Summary of Product Characteristics. Novartis Europharm Ltd. **3.** Cockcroft DW, Gault MH. *Nephron*. 1976;16(1):31-41. **4.** Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. *Ann Intern Med*. 2012;156(11):785-795. **5.** 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. **6.** Schwartz GJ, Brion LP, Spitzer A. *Pediatr Clin North Am*. 1987;34(3):571-590.

Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to:

Medicines Authority Post-licensing Directorate,
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann. SGN 3000.

Or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events suspected to be associated with the use of Exjade to Novartis Pharma Services Inc., Representative Office, Malta, by phone on 21222872, by fax on 22487219 or e-mail at drug_safety.malta@novartis.com.

Marketing Authorisaiton Holder: Novartis Europharm Limited, Frimley Business Park, Camberley, Surrey GU16 7S4, United Kingdom.

Local Representative: Novartis Pharma Services Inc., Representative Office Malta. Tel No.: +356 21222872

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

April 2018 EXJ HCP 04/18 MT