Important Information to Remember About Exjade/Jadenu (deferasirox) Physician guide

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

Exjade EU RMP V17.1 Feb 2021

Objectives

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks

please advised to be read carefully before prescribing/dispensing/administering the product.

Indications[1]

Chronic Transfusional Iron Overload

Exjade/Jadenu (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. Exjade/Jadenu (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

Exjade/Jadenu (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]

- Exjade/Jadenu (deferasirox) is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients
- Exjade/Jadenu (deferasirox) is contraindicated for use in combination with other iron chelator therapies as the safety of such combinations has not been established
- Exjade/Jadenu (deferasirox) is contraindicated in patients with estimated CrCl <60 ml/min
  - Exjade/Jadenu (deferasirox) has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min

Starting Exjade/Jadenu (deferasirox) treatment

Before initiating therapy

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

Dose comparisons between Exjade/Jadenu (deferasirox)® film-coated tablets and dispersible tablets

There are different formulations of Exjade/Jadenu (deferasirox) : Exjade/ Jadenu (deferasirox) film-coated tablets and Exjade/Jadenu (deferasirox) dispersible tablets, each available in three strengths[1]

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

All formulations have the same active ingredient (Exjade/Jadenu (deferasirox)).

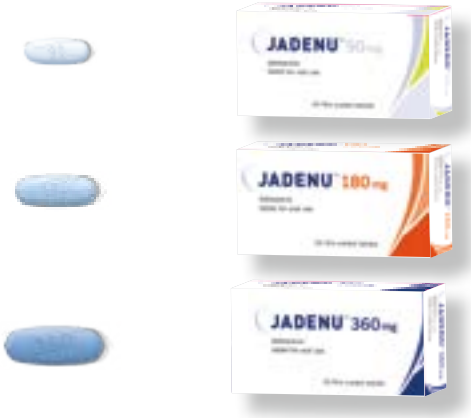
- Exjade/Jadenu (deferasirox) film-coated tablets are a strength-adjusted formulation of Exjade/Jadenu (deferasirox) , with higher bioavailability than the dispersible tablets
- Formulations are differentiated by form and/or color and/or size and/or packaging

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

Important differences between Exjade/Jadenu (deferasirox) film-coated tablets, and dispersible tablets

Exjade/Jadenu (deferasirox) film-coated tablets[1,2]

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/ Jadenu (deferasirox) film-coated tablets may be crushed and administered by sprinkling onto soft food (eg, yogurt or applesauce)	Does not contain lactose



Exjade/Jadenu (deferasirox) dispersible tablets[1]

Strengths: 125 mg 250 mg 500 mg (round, off-white tablets)	Must be taken on an empty stomach, at least 30 minutes before food Disperse tablets in water, orange juice, or apple juice. Dispersible tablets must not be chewed or swallowed whole	Contains lactose

Tablets displayed are not actual size.

Dose comparisons between Exjade/Jadenu (deferasirox)® film-coated tablets and dispersible tablets (continued)

Converting from dispersible tablets to film-coated tablets[1]

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

Dose comparisons between Exjade/Jadenu (deferasirox) film-coated tablets and dispersible tablets

Exjade/Jadenu (deferasirox) film-coated tablets[1,2]	dispersible tablets[1]
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/Jadenu (deferasirox) ® film-coated tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 14 mg/kg/day body weight[1,2]
- Doses >28 mg/kg/day are not recommended[1]
- Monitor your patients regularly[1]

(Exjade/Jadenu (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, or 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, or closely monitor renal and hepatic function andserum ferritin levels	
Patients already well managed on treatment with deferoxamine A starting dose of Exjade/Jadenu (deferasirox) film-coated tablets that is numerically one third that of the deferoxamine dose could be considered	Increase in increments of 3.5 to 7 mg/kg/day if dose is <14 mg/kg body weight 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, or closely monitor renal and hepatic function andserum ferritin levels	

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[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 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/Jadenu (deferasirox) ® film-coated tablets dosing for patients with chronic transfusional iron overload

- 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/Jadenu (deferasirox) is recommended for patients with NTDT[1]
- Monitor your patients regularly[1]

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

INITIATE therapy	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 to7 mg/kg/day or less, or closely monitor renal and hepatic function and serum ferritin levels	There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and, therefore, retreatment cannot be recommended
LIC ≥5 mg Fe/g dw OR SF consistently >800 µg/l	**LIC ≥7 mg Fe/g dw OR SF consistently >2000 µg/lb**	**LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l**	**GOAL LIC <3 mg Fe/g dw OR SF consistently <300 µg/l**

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

[a]Doses above 20 mg/kg/day are not recommended for patients with NTDT. In patients in whom LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 10 mg/kg.

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

Pediatric NTDT patients1

In pediatric patients, dosing should not exceed 7 mg/kg/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, Exjade/Jadenu (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 Exjade/Jadenu (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.

Exjade/Jadenu (deferasirox)® dispersible tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 20 mg/kg/day body weight[1,2]
- Doses >28 mg/kg/day are not recommended[1]
- Monitor your patients regularly[1]

Exjade/Jadenu (deferasirox) dispersible 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
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 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, or 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, or closely monitor renal and hepatic function andserum ferritin levels	
Patients already well managed on treatment with deferoxamine Starting dose of Exjade/Jadenu (deferasirox) 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, or closely monitor renal and hepatic function and serum ferritin levels	

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[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 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/Jadenu (deferasirox)® dispersible 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/Jadenu (deferasirox) is recommended for patients with NTDT[1]
- Monitor your patients regularly[1]

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

INITIATE therapy	UP-TITRATE to achieve target SF when necessary[a,b]	DOWN-TITRATE to avoid overchelation	STOP therapy once target SF has been achieved
10 mg/kg/day	Increase in increments of 5 to 10 mg/kg/day	Decrease dose to 10 mg/kg/day or less, or closely monitor renal and hepatic function and serum ferritin levels	Retreatment is not recommended fo 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/lb**	**LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l**	**GOAL LIC <3 mg Fe/g dw OR SF consistently <300 µg/l**

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

[a]Doses above 20 mg/kg/day are not recommended for patients with NTDT. In patients in whom LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 10 mg/kg.

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

Pediatric NTDT patients1

In pediatric patients, dosing should not exceed 10 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, Exjade/Jadenu (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 Exjade/Jadenu (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 of Exjade/Jadenu (deferasirox) [1]

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	Abnormalities in levels of tubular markers and/or if clinically indicated—also refer patient to renal specialist and consider biopsy (also consider dose reduction)
Serum transaminase	Persistent and progressive increase in liver enzyme
Metabolic acidosis	Development of metabolic acidosis
SJS, 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.

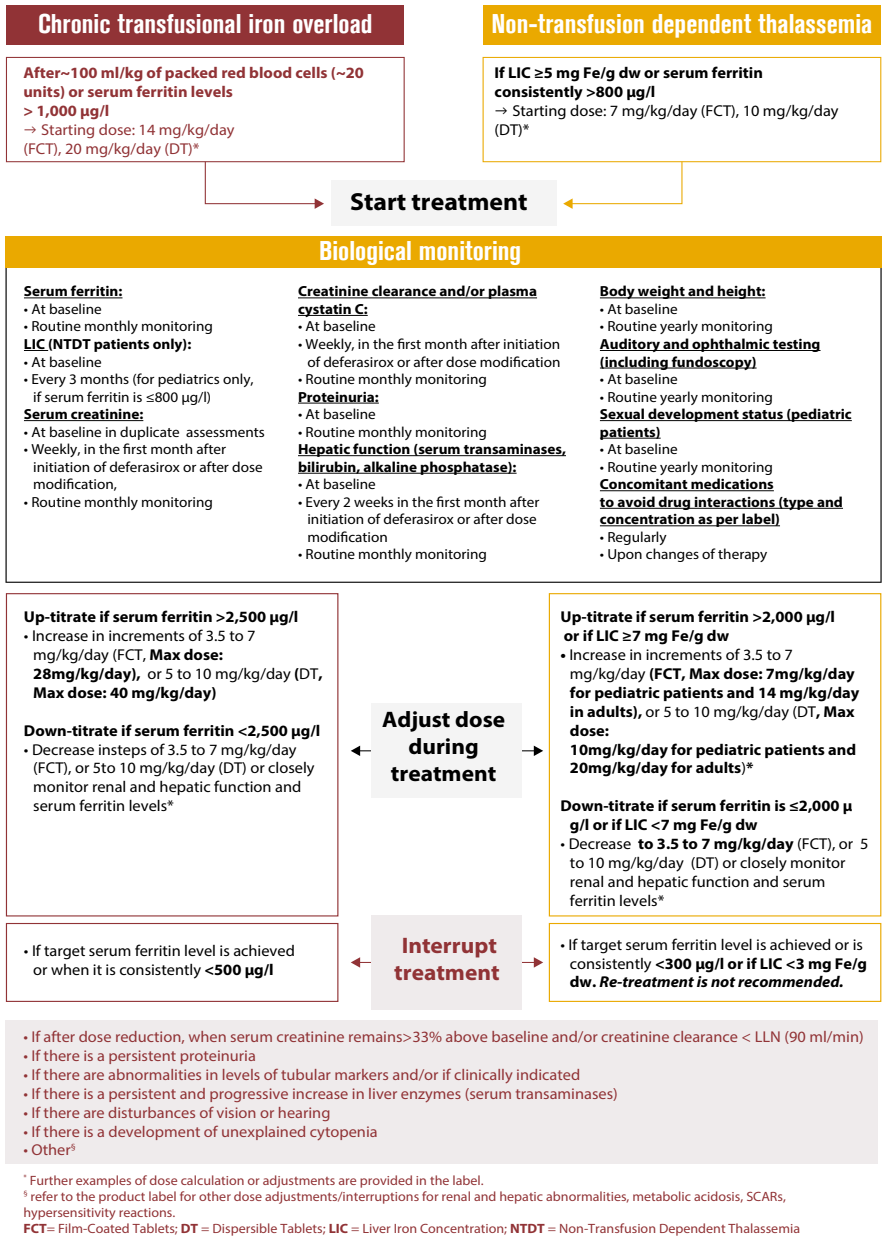
Monitoring recommendations for patients prior to and during Exjade/Jadenu (deferasirox) treatment[1]

	Baseline	In the first month after initiation of Exjade/ Jadenu (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	✓				✓
Auditory/ophthalmic testing (including funduscopy)	✓				✓
sexual development	✓				✓

[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.

Physician's reference checklist for deferasirox dosing and biological monitoring



* Further examples of dose calculation or adjustments are provided in the label.
[5] refer to the product label for other dose adjustments/interruptions for renal and hepatic abnormalities, metabolic acidosis, SCARs, hypersensitivity reactions.
FCT= Film-Coated Tablets; **DT** = Dispersible Tablets; **LIC** = Liver Iron Concentration; **NTDT** = Non-Transfusion Dependent Thalassemia

Renal safety profile

Findings from clinical trials

Parameters measured in clinical trials[1]

In Exjade/Jadenu (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 Exjade/Jadenu (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 Exjade/Jadenu (deferasirox) (including switch of formulation), and monthly thereafter.**

Renal safety profile

Methods for estimating CrCl[1]

For your reference, here is a brief overview of methods to estimate CrCl in adults and children when prescribing Exjade/Jadenu (deferasirox) .

Adult

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

Cockcroft–Gault formula[3]

The Cockcroft-Gault formula employs 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

Exjade/Jadenu (deferasirox) ® (Exjade/Jadenu (deferasirox)) film-coated tablets: Reduce the dose by 7 mg/kg/day, if Exjade/Jadenu (deferasirox) ® (Exjade/Jadenu (deferasirox)) dispersible tablets: Reduce the dose by 10 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 there are abnormalities
- Renal tubulopathy has been mainly reported in children and adolescents with β-thalassemia treated with Exjade/Jadenu (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 Exjade/Jadenu (deferasirox) therapy, particularly in children

Hepatic safety profile

Liver function assessment

Liver function test elevations have been observed in patients treated with Exjade/Jadenu (deferasirox)

- Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with Exjade/Jadenu (deferasirox)
- Most reports of hepatic failure involved patients with significant morbidities including preexisting liver cirrhosis
- However, the role of Exjade/Jadenu (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

Recommendations in hepatic impairment

Exjade/Jadenu (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 Exjade/Jadenu (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 Exjade/Jadenu (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 Exjade/Jadenu (deferasirox) therapy, particularly in children

References: 1. Exjade/Jadenu (deferasirox) ® dispersible tablets [EU Summary of Product Characteristics]. Novartis; November 2017. 2. JADENU® film coated tablets [Prescribing Information]. Novartis; July 2018. 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.

JADENU®

Important note: Before prescribing, consult full prescribing information.

Presentation:

JADENU film-coated tablets

Film-coated tablets containing 90 mg, 180 mg or 360 mg of deferasirox.

Indications: JADENU 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 thalassaemia major aged 6 years and older.

JADENU 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 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.

JADENU is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with nontransfusiondependent thalassaemia syndromes aged 10 years and older.

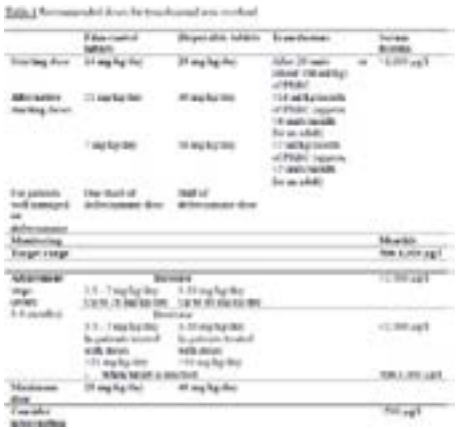
Dosage:

Treatment with JADENU should be initiated and maintained by physicians experienced in the treatment
of chronic iron overload.

Transfusional iron overload

It is recommended that treatment be started after the transfusion of approximately 20 units (about
100 ml/kg) of packed red blood cells (PRBC) or when there is evidence from clinical monitoring that
chronic iron overload is present (e.g. serum ferritin >1,000 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. JADENU film-coated tablets demonstrate higher bioavailability compared to the JADENU dispersible tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet. The corresponding doses for both formulations are shown in the table below.



Starting dose

The recommended initial daily dose of JADENU film-coated tablets is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg may be considered for patients who require reduction of elevated body
iron levels and who are also receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult).An initial daily dose of 7 mg/kg may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.For patients already well managed on treatment with deferoxamine, a starting dose of JADENUfilm-coated tablets that is numerically one third that of the deferoxamine dose could be considered (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 14 mg/kg/day of JADENU film-coated tablets). When this results in a daily dose less than 14 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of JADENU be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). 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 28 mg/kg may be considered. The availability of long-term efficacy and safety data with JADENU dispersible tablets used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 21 mg/kg, a further increase (to a maximum of 28 mg/kg) may not achieve
satisfactory control, and alternative treatment options may be considered. If no satisfactory control is
achieved at doses above 21 mg/kg, treatment at such doses should not be maintained and alternative
treatment options should be considered whenever possible. Doses above 28 mg/kg are not recommended
because there is only limited experience with doses above this level.

In patients treated with doses greater than 21 mg/kg, dose reductions in steps of 3.5 to 7 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target
(usually between 500 and 1,000 µg/l), dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

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.

JADENU film-coated tablets demonstrate higher bioavailability compared to the JADENU dispersible
tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets,
the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded
to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Starting dose

The recommended initial daily dose of JADENU film-coated tablets in patients with non-transfusion-dependent thalassaemia syndromes is 7 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 3.5 to 7 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 14 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 7 mg/kg. For patients in whom the dose was increased to >7 mg/kg, dose reduction to 7 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.

Special populations

Elderly patients (≥65 years of age)

The dosing recommendations for elderly patients are the same as described above. In clinical studies,elderly patients experienced a higher frequency of adverse reactions than younger patients (in particular,diarrhoea) and should be monitored closely for adverse reactions that may require a dose adjustment.

Paediatric population

Transfusional iron overload:

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. Non-transfusion-dependent thalassaemia syndromes: In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 7 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. Children from birth to 23 months: The safety and efficacy of JADENU in children from birth to 23 months of age have not been established.No data are available. *Patients with renal impairment* JADENU has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min. *Patients with hepatic impairment* JADENU is not recommended in patients with severe hepatic impairment (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% (see sections 4.4 and 5.2), and JADENU 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. Method of administration For oral use. The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use. The film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal.

Contraindications:

♦Hypersensitivity to the active substance or to any of the excipients. ♦ Combination with other iron chelator therapies as the safety of such combinations has not been established. ♦Patients with estimated creatinine clearance <60 ml/min.

Women of child-bearing potential, pregnancy, breast-feeding and fertility: ♦Pregnancy: No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. As a precaution, it is recommended that JADENU not be used during pregnancy unless clearly necessary. **♦Breast-feeding:** It is not known if deferasirox is secreted into human milk. Breast-feeding while taking JADENU is not recommended. **♦Fertility:** No fertility data is available for humans. In animals, no adverse effects on male or female fertility were found.

Warnings/Precautions: ♦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). ♦Increased risk of renal adverse events with filmcoated tablets doses above 21 mg/kg cannot be excluded. ♦Serum creatinine, creatinine clearance and/or plasma cystatin C levels should be monitored prior to therapy, weekly in the first month after initiation or modification of therapy with JADENU (including switch of formulation), and monthly thereafter. ♦Interruption of JADENU therapy should be considered in patients who develop metabolic acidosis. ♦Dose reduction or interruption may be 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 betathalassaemia treated with JADENU. ♦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). ♦ It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. ♦If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, JADENU should be interrupted. ♦JADENU is not recommended in patients with severe hepatic impairment. ♦Treatment with JADENU is not recommended in patients with a short life expectancy, especially when comorbidities could increase the risk of adverse events. ♦Caution in elderly patients due to a higher frequency of adverse reactions. ♦JADENU therapy should be closely monitored to detect adverse reactions and to follow iron burden in the paediatric population. ♦Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during JADENU therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. ♦Caution should be exercised in patients who are taking JADENU in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm^3 (^{50} x 109/l). ♦Skin rashes may appear during JADENU treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. ♦If SJS or any other severe skin reaction is suspected, JADENU should be discontinued immediately and should notbe reintroduced. ♦Cases of serious hypersensitivity reactions have been reported in patients receiving deferasirox If such reactions occur, JADENU should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock. ♦Auditory and ophthalmic testing is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered. ♦Interruption of treatment should be considered in patients who develop unexplained cytopenia. ♦Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy. If serum ferritin falls consistently below 500 µg/l (in transfusional iron overload) or below 300 µg/l (in nontransfusiondependent thalassaemia syndromes), an interruption of treatment should be considered. ♦The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends. ♦In the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored prior to therapy and at regular intervals (every 12 months). ♦Cardiac function should be monitored in patients with severe iron overload during longterm treatment with JADENU.

Interactions: ♦ Deferasirox must not be combined with other iron chelator therapies. ♦JADENU filmcoated tablets may be taken either on an empty stomach or with a light meal, preferably at the same time each day. ♦The patient's serum ferritin should be monitored during and after the combination, and the dose of JADENU adjusted if necessary when concomitantly used with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir). ♦Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling. ♦Caution when combined with drugs metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents, bepridil, ergotamine,). ♦The concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed. Interaction with other CYP2C8 substrates like paclitaxel cannot be excluded. ♦Consider monitoring of theophylline concentration and possible theophylline dose reduction. Interaction with 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. ♦It is not recommended to take deferasirox with aluminium-containing antacids. ♦Caution when combined with drugs with ulcerogenic potential (e.g. NSAIDS, corticosteroids, oral bisphosphonates) or with anticoagulants.

Adverse reactions: ♦***Very common*** (≥1/10): blood creatinine increased. ♦***Common***(≥1/100 to <1/10): headache, diarrhea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, transaminases increased, rash, pruritus, proteinuria.

♦***Uncommon***(≥1/1,000 to <1/100): anxiety, sleep disorder, dizziness, cataracts, maculopathy, deafness, laryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder (acquired Fanconi syndrome), glycosuria, pyrexia, oedema, fatigue. ♦***Rare*** (≥1/10,000 to <1/1,000): optic neuritis, esophagitis. ♦***Not known***: Pancytopenia, thrombocytopenia, anaemia aggravated, neutropenia, hypersensitivity reactions (including anaphylactic reactions and angioedema), metabolic acidosis, gastrointestinal perforation, acute pancreatitis, hepatic failure, StevensJohnson syndrome, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, nephrolithiasis, renal tubular necrosis,

Version: 3.1

EXJADE®

Important note: Before prescribing, consult full prescribing information.

Presentation:

***Exjade®* dispersible tablets**

Dispersible tablets containing 125 mg, 250 mg or 500 mg of deferasirox.

Indications: Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).

Exjade is also indicated for the treatment of chronic iron overload in patients with nontransfusion-dependent thalassemia syndromes aged 10 years and older.

Dosage: Transfusional iron overload

It is recommended that therapy with Exjade be started after the transfusion of approximately

20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 microgram/L).

Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

10 mg per kilogram body weight for pediatric patients not receiving regular blood transfusions

♦**Starting daily dose:**

Exjade dispersible tablets

The recommended initial daily dose of Exjade is 20 mg/kg body weight.

An initial daily dose of 30 mg/kg may be considered for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately >4 units/month for an adult), and for whom the objective is reduction of iron overload.

An initial daily dose of 10 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult), and for whom the objective is maintenance of the body iron level.

For patients already well-managed on treatment with deferoxamine, a starting dose of Exjade that is numerically half that of the deferoxamine dose could be considered as shown in tables

1 and 3 (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 20 mg/kg/day of Exjade).

♦**Monthly monitoring of serum ferritin** for assessing patient's response to therapy.

♦**Dose adjustment:**

It is recommended that serum ferritin be monitored every month and that the dose of Exjade is adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above

2,500 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below

500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Exjade may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section WARNINGS AND PRECAUTIONS).

♦**Maximum daily dose:**

Exjade dispersible tablets

The maximum daily dose of dispersible tablets is 40 mg/kg body weight.

Dosage: Non-transfusion-dependent thalassemia syndromes and iron overload

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 microgram/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation.

♦**Starting daily dose:**

Exjade dispersible tablets

The recommended initial daily dose of Exjade is 10 mg/kg body weight.

♦**Dose adjustment:**

It is recommended that serum ferritin be monitored every month. Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's LIC is

≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 microgram/L and not showing a downward trend, and the patient is tolerating the drug 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 thalassemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 microgram/L, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction is recommended to 10 mg/kg or less when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 microgram/L.

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin

<300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

♦**Maximum daily dose:**

Exjade dispersible tablets

The maximum daily dose of dispersible tablets is 20 mg/kg body weight.

Administration:

Exjade dispersible tablets

Exjade must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

Contraindications: Creatinine clearance <40 mL/min or serum creatinine >2 times the age appropriate upper limit of normal.

High risk myelodysplastic syndrome (MDS) patients and patients with other haematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

Hypersensitivity to the active substance or to any of the excipients.

Women of child-bearing potential, pregnancy, breast-feeding and fertility: ♦**Pregnancy:** No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. As a precaution, it is recommended that Exjade not be used during pregnancy unless clearly necessary. ♦**Breast-feeding:** In animal studies, deferasirox was found to be rapidly and extensively secreted into maternal milk. No effects on the offspring were noted at maternally non-toxic doses of deferasirox. It is not known if deferasirox is secreted into human milk. Breast-feeding while taking Exjade is not recommended.♦**Fertility:** EXJADE did not affect fertility or reproduction in rat studies even at toxic doses.

Warnings/Precautions: The decision to remove accumulated iron should be individualized based on anticipate clinical benefit and risks of chelation therapy. Caution should be used in elderly patients due to a higher frequency of adverse reactions.

Renal impairment

Non-progressive rises in serum creatinine have been noted in patients treated with Exjade, usually within the normal range. This has been observed in both pediatric and adult patients with iron overload during the first year of treatment. A study which assessed the renal function of patients enrolled in the registration studies up to 13 years later, confirmed the nonprogressive nature of these serum creatinine observations.

Cases of acute renal failure have been reported following the post-marketing use of Exjade. Although causal relationship with Exjade could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy and monitored monthly thereafter. Patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function may be more at risk of complications. Therefore, serum creatinine and/or creatinine clearance should be monitored weekly in the first month after initiation or modification of therapy (including switching formulation), and monthly thereafter. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

Renal tubulopathy has been reported in patients treated with Exjade. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 microgram/L.

Tests for proteinuria should be performed monthly.

Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting. For adult patients, the daily dose of Exjade may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section. For pediatric patients, the dose may be reduced by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits. If there is a progressive increase in serum creatinine beyond the upper limit of normal, Exjade should be interrupted. Therapy with Exjade may be reinitiated depending on the individual clinical circumstances.

Hepatic impairment

Exjade is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Exjade treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox was not influenced by such transaminase levels. Deferasirox is principally eliminated by

glucuronidation and is minimally (about 8%) metabolized by oxidative cytochrome P450 enzymes.

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials. There have been post-marketing reports of hepatic failure in patients treated with Exjade. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients. It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, Exjade should be interrupted. Once the cause of the liver function test abnormalities has been clarified orafter return to normal levels, cautious re-initiation of Exjade treatment at a lower dose followed by gradual dose escalation may be considered.

Blood disorders

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with Exjade. Most of these patients had pre-existing hematologic disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with Exjade is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with Exjade should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with Exjade may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal disorders

Gastrointestinal irritation may occur during Exjade treatment. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Exjade. There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients.

Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Exjade therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

Caution should be exercised in patients who are taking Exjade in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see section INTERACTIONS), and in patients with platelet counts <50 x 109/L.

Hypersensitivity reactions

Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Exjade, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, Exjade should be discontinued and appropriate medical intervention instituted. Exjade should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

Skin disorders

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported during the post-marketing period. The risk of other skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If severe skin reactions are suspected Exjade should be discontinued immediately and should not be reintroduced.

Rare cases of erythema multiforme have been reported during Exjade treatment.

Skin rashes may appear during Exjade treatment. For rashes of mild to moderate severity,

Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Exjade may be re-introduced after resolution of the rash, at a lower dose followed by gradual dose escalation.

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with

Exjade treatment. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Exjade treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.

Other considerations

As with other iron chelator treatment, the risk of toxicity of Exjade may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

Exjade has not been associated with growth retardation in children followed for up to 5 years in clinical trials. However, as a general precautionary measure, body weight and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

The dispersible tablets contain lactose (1.1 mg lactose for each mg of deferasirox). This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

Driving and using machines

No studies on the effects of Exjade on the ability to drive and use machines have been performed. Patients experiencing the uncommon adverse effect of dizziness should exercise caution when driving or operating machines.

Interactions:

Agents that may decrease Exjade systemic exposure

In a healthy volunteer study, the concomitant administration of Exjade (single dose of 30 mg/kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% to 51%). Therefore, the concomitant use of Exjade with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade efficacy. If Exjade and a potent UGT inducer are used concomitantly, increases in the dose of Exjade should be considered based on clinical response to therapy.

Interaction with food

The bioavailability of deferasirox was increased to a variable extent when taken along with food. Exjade must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day.

Interaction with midazolam and other agents metabolized by CYP3A4

In a healthy volunteer study, the concomitant administration of Exjade and midazolam (a

CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% to 26%). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined withsubstances metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

Interaction with repaglinide and other agents metabolized by CYP2C8

In a healthy volunteer study, the concomitant administration of Exjade (repeated dose of

30 mg/kg/day) and the CYP2C8 substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide AUC and Cmax by 131% (90% CI: 103% to 164%) and 62% (90% CI: 42% to 84%), respectively. When Exjade and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between Exjade and other

CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolized by CYP1A2

In a healthy volunteer study, the concomitant administration of Exjade (repeated dose of

30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84% (90% CI: 73% to 95%). The single dose Cmax was not affected, but an increase of theophylline Cmax is expected to occur with chronic dosing. When

Exjade and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between

Exjade and other CYP1A2 substrates may be possible.

Other Information

No interaction was observed between Exjade and digoxin in healthy volunteers.

The concomitant administration of Exjade and vitamin C has not been formally studied.

Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences.

The safety profile of deferasirox in combination with other iron chelators (deferoxamine,

deferiprone) observed in clinical trials, post-marketing experience or published literature (as applicable) was consistent with that characterized for monotherapy.

The concomitant administration of Exjade and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, Exjade tablets must not be taken with aluminum-containing antacid preparations.

Concomitant administration of Exjade with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of Exjade in patients receiving anticoagulants may increase the risk of gastrointestinal irritation.

EXJADE must not be taken with other iron chelators.

Adverse reactions: ♦***Very common***: blood creatinine increased. ♦***Common***: nausea, vomiting, diarrhea, abdominal pain, abdominal distension, constipation, dyspepsia, rash, pruritus, transaminases increased, proteinuria, headache. ♦***Uncommon***: anxiety, sleep disorder, dizziness, cataracts, maculopathy, deafness, laryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder(Fanconi syndrome), pyrexia, edema, fatigue. ♦***Rare***: optic neuritis, erythema multiforme, esophagitis. ♦***Adverse drug reactions from post-marketing (frequency unknown)***: renal tubular necrosis, , Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, hepatic failure, hypersensitivity vasculitis, urticaria, alopecia, hypersensitivity reaction (including anaphylactic reaction and angioedema).

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Patient Safety Department Novartis Pharma AG - Saudi Arabia -.
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Fax: +966112658107
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Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Fax: +966112057662
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

NOVARTIS
Novartis Saudi Limited نوفارتس السعودية ليميتد
Tamkeen Tower , Olia Street, Al Yasmine District Building Number: 7252
(P.O Box 16032, Riyadh 11464 Saudi Arabia)
Tel: +966112658100, Fax: +966 11 464 8127