Important Information to Remember About Exjade/Jadenu (deferasirox)

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

EU RMP V 16.2 / June 2019

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

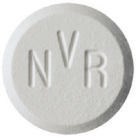
A different posology and method of administration must be applied when switching patients from dispersible tablets to film-coated tablets of Exjade/Jadenu (deferasirox) .

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  90 mg  180 mg  360 mg

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  125 mg  250 mg  500 mg

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.

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.**

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

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) = $141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}}$ × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

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 and sprinkle granules [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 non transfusion dependent 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	**Film-Coated Tablets**	**Dispersible tablets**	**Transfusions**		**Serum ferrittin**
Starting dose	**14 mg/kg/day**	**20mg/kg/day**	**After20 units (about 100 ml/kg) of PRBC**	**or**	**> 1,000 µg/l**
Alternative starting dose	**21mg/kg/day**	**30mg/kg/day**	**> 14 ml/kg/month of PRBC (approx.<4units/ month for an adult)**		
	7mg/kg/day	**10mg/kg/day**	**< 7 ml/kg/month of PRBC (approx. <2units/month for an adult)**		
For patients well managed on deferoxamine	**One third of deferoxamine dose**	**Half of deferoxamine dose**			
Monitoring					**Monthly**
Target range					**500-1,000 µg/l**
Adjestment Steps (every 3-6 months)	**Increase**				**<2,500 µg/l**
	3.5 – 7 mg/kg/day up to 28mg/ kg/day	**5 mg/kg/dayup to 40mg/kg/day**			
	Decrease				**<2,500 µg/l**
	3.5 – 7 mg/kg/day in patients treated with dose > 21 mg/kg/day	**5-10 mg/kg/day in patients treated with dose > 30 mg/kg/day**			
	When target is reached				**500-1,000 µg/l**
Maximum dose	**21mg/kg/day**	**40mg/kg/day**			
Consider interruption					**< 500µg/l**

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.

	Film-Coated Tablets	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferrittin**
Starting dose	**7mg/kg/day**	**10mg/kg/day**	**≥ mg/g dw**	**or**	**> 800 µg/l**
Monitoring					**Monthly**
Adjestment Steps (every 3-6 months)	**Increase**		**≥7mg Fe/g dw**	**or**	**>2,000 µg/l**
	3.5–7mg/kg/day	**5-10mg/kg/day**			
	Decrease		**<7mg Fe/g dw**	**or**	**≤2,000 µg/l**
	3.5–7mg/kg/day	**5-10mg/kg/day**			

Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10mg/kg/day**			
	For adults **For paediatric patients**		**Not assessed**	**and**	**≤2,000 µg/l**
interruption			**<3mg Fe/g dw**	**or**	**<300 µg/l**
Retreatment			**Not recommended**		

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 toswallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the fulldose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately andcompletely 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 film coated 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 beta thalassaemia 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 co morbidities 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/mm3 (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 not be 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 non transfusion dependent 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 long term treatment with JADENU. **Interactions:** • Deferasirox must not be combined with other iron chelator therapies. •JADENU film coated 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, Stevens Johnson 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: dispersible tablets containing 125 mg, 250 mg or 500 mg of deferasirox.
Indications: • for adults and pediatric patients aged 10 years and over with chronic iron overload due to blood transfusions (transfusional hemosiderosis). • for adults and pediatric patients aged 10 years and over with non-transfusion-dependent thalassemia syndromes and iron overload.

Dosage: Transfusional iron overload • Starting daily dose: recommended initial daily dose is 20 mg/kg body weight; consider 30 mg/kg for patients receiving >14 mL/kg/month of packed red blood cells (>4 units/month), and for whom the objective is the reduction of iron overload; consider 10 mg/kg for patients receiving <7 mL/kg/month of packed red blood cells (<2 units/month), and for whom the objective is the 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. 50% starting dose reduction in moderate hepatic impairment (Child-Pugh B). Should not be used in severe hepatic impairment (Child-Pugh C). • Monthly monitoring of serum ferritin for assessing patient's response to therapy. • Dose adjustment 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.

Dosage: Non-transfusion-dependent thalassemia syndromes and iron overload • Starting daily dose: recommended initial daily dose is 10 mg/kg body weight. 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. • Dose adjustment should be considered every 3 to 6 months in steps 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. 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. • 50% starting dose reduction in moderate hepatic impairment (Child-Pugh B). Should not be used in severe hepatic impairment (Child-Pugh C). • Maximum daily dose is 20 mg/kg body weight.

Administration: EXJADE must be taken once daily on an empty stomach at least 30 minutes before food. • EXJADE tablets to be dispersed in water or apple or orange juice.

Contraindications: • Hypersensitivity to deferasirox or to any of the excipients. • Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal. • High risk MDS patients and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

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: 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: • Caution in elderly patients due to a higher frequency of adverse reactions. • Caution 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. Monthly monitoring of creatinine clearance, serum creatinine and proteinuria: dose reduction may be needed in some cases of non-progressive increase in serum creatinine; EXJADE should be interrupted if serum creatinine shows a progressive rise beyond the age-appropriate upper limit of normal. More frequent creatinine monitoring recommended in patients with an increased risk of renal complications. Rare reports of acute renal failure, some of which required dialysis. Reports of renal tubulopathy mainly in children with beta-thalassemia and serum ferritin levels <1,500 microgram/L. • Not recommended in patients with severe hepatic impairment (Child-Pugh C). 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. Post-marketing cases of hepatic failure have been reported. • Gastrointestinal irritation may occur. Upper gastrointestinal ulceration and hemorrhage 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 hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 x 109/L. • Cases of Stevens-Johnson syndrome (SJS) have been reported during the post-marketing period. If SJS is suspected EXJADE should be discontinued. • Skin rashes: EXJADE should be interrupted if severe rash develops. • Discontinue if severe hypersensitivity reaction occurs.
• Annual ophthalmological/audiological testing. • Should not be used during pregnancy unless clearly necessary. • Not recommended when breast-feeding. • Must not be combined with other iron chelator therapies. • Product contains lactose.

Interactions: • Should not be taken with aluminium-containing antacids. • Caution when combined with drugs metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents, midazolam). • Increases in the dose of Exjade should be considered when concomitantly used with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir). • Careful monitoring of glucose levels should be performed when repaglinide is used concomitantly with EXJADE. 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 may be possible. • Caution when combined with drugs with ulcerogenic potential (e.g. NSAIDS, corticosteroids, oral bisphosphonates) or with anticoagulants.

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, early cataracts, maculopathy, hearing loss, pharyngolaryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubulopathy (Fanconi's syndrome), pyrexia, edema, fatigue. • Rare: optic neuritis, erythema multiforme, esophagitis. • Adverse drug reactions from post-marketing (frequency unknown) : Stevens-Johnson syndrome, acute renal failure, tubulointerstitial nephritis, hepatic failure, leukocytoclastic vasculitis, urticaria, alopecia, hypersensitivity reactions (including anaphylaxis and angioedema), aggravated anemia and cytopenia (relationship with EXJADE uncertain).

Packs and Prices: Country specific.
Legal classification: Country specific.

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