NON-TRANSFUSION-DEPENDENT THALASSEMIA (NTDT)

EXJADE® (deferasirox) Dosing and Monitoring Guidelines for NTDT Patients with Iron Overload

EXJADE® deferasirox

Key elements of the physician information for use of EXJADE in NTDT patients with chronic 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 [SF] consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available. The recommended initial daily dose of EXJADE in patients with NTDT syndromes is 10 mg/kg body weight.
- Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or SF <300 µg/l), treatment should be stopped.
- Caution should be taken during chelation therapy to minimize the risk of overchelation in all patients.
- In pediatric patients with NTDT syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and SF is essential to avoid overchelation: in addition to monthly SF assessments, LIC should be monitored every 3 months when SF is ≤800 µg/l.
- Long-term safety of deferasirox in pediatric patients with NTDT has not been evaluated; therefore, close monitoring is needed in order to detect side effects.
- 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.

EXJADE DOSING AND MONITORING GUIDELINES FOR NTDT PATIENTS WITH IRON OVERLOAD

NTDT

Therapeutic indications for EXJADE

Indication for NTDT

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

EXJADE is also indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with β-thalassemia major aged 6 years and older.

EXJADE 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 patients with β-thalassemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with β-thalassemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
- in patients with other anemias aged 2 years and older.

EXJADE® deferasirox

STARTING EXJADE TREATMENT IN NTDT PATIENTS WITH IRON OVERLOAD

NTDT

Measure SF or LIC before initiating therapy

Chelation therapy should only be initiated when there is evidence of iron overload	**LIC ≥5 mg Fe/g dw OR SF >800 µg/l**
Recommended initial daily dose	**10 mg/kg/day body weight**

Measure iron overload with LIC

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.

Only one course of treatment with EXJADE is recommended for patients with NTDT.

EXJADE dosing for NTDT patients

INITIATE chelation therapy 10 mg/kg/day	UP-TITRATE to achieve goal when necessary	DOWN-TITRATE to avoid overchelation	STOP once goal achieved
Monitor monthly	Increase in increments of 5 to 10 mg/kg/day up to 20 mg/kg/day[a]	Decrease dose to 10 mg/kg/day	Retreatment is not recommended for patients with NTDT
LIC ≥5 mg Fe/g dw OR SF >800 µg/l	LIC ≥7 mg Fe/g dw OR SF >2000 µg/l[b]	LIC <7 mg Fe/g dw OR SF ≤2000 µg/l	**GOAL** LIC <3 mg Fe/g dw OR SF <300 µg/l

[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 LIC and SF levels are not showing a downward trend and the patient is tolerating the medical product well.

Pediatric NTDT patients

In patients 10 to 17 years of age, 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.

EXJADE® deferasirox

MONITOR EXJADE TREATMENT FOR OPTIMAL RESULTS

NTDT

Recommended monitoring during EXJADE treatment

	Baseline	In the first month after initiation of EXJADE	Monthly	Every 3 months	Yearly
SF	✓		✓		
LIC	✓			✓ (for pediatric patients only, if SF is ≤800 µg/l)	✓
Serum creatinine	2x	Weekly	✓		
Creatinine clearance		Weekly (or plasma cystatin C)	✓ (or plasma cystatin C)		
Proteinuria			✓		
Serum transaminases, bilirubin, alkaline phosphatase	✓	Every 2 weeks	✓		
Body weight, height, and sexual development (pediatric patients)					✓
Auditory/ ophthalmic testing (including fundoscopy)	✓				✓

Contraindications

EXJADE is contraindicated in:

- patients with hypersensitivity to the active substance or the following excipients: lactose monohydrate; crospovidone type A; cellulose, microcrystalline; povidone; sodium lauryl sulfate; silica, colloidal anhydrous; magnesium stearate.
- combination with other iron chelator therapies as the safety of such combinations has not been established.
- patients with estimated creatinine clearance <60 ml/min.

WARNING

Data in children with NTDT are very limited. As a consequence, EXJADE therapy should be closely monitored to detect side effects and to follow iron burden in the pediatric population. In addition, before treating heavily iron-overloaded children with NTDT with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

EXJADE® deferasirox

EXJADE® (deferasirox) dispersible tablets

PRESENTATION: dispersible tablets containing 250 mg or 500 mg deferasirox.

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

DOSAGE AND ADMINISTRATION: Transfusional iron overload ♦ Starting daily dose: 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 for adults), and for whom the objective is reduction of iron overload; consider 10 mg/kg for patients receiving <7 ml/kg/month of packed red blood cells (<2 units/month for adults), and for whom the objective is maintenance of the body iron level**;** for patients already well-managed on treatment with deferoxamine, consider a starting dose of EXJADE® that is numerically half that of the deferoxamine dose. ♦ Monthly monitoring of serum ferritin for assessing patient's response to therapy ♦ **Dose adjustment:** to be adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 to 10 mg/kg. In patients not adequately controlled with doses of 30 mg/kg, doses of up to 40 mg/kg may be considered. In patients whose serum ferritin level has reached the target (usually between 500 and 1000 microgram/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. EXJADE® should be interrupted if serum ferritin falls consistently below 500 micrograms/l. ♦ **Maximum daily dose** is 40 mg/kg body weight. **Paediatric patients:** dosing is the same as for adults. However change in weight of patients must be taken into account when calculating the dose. ♦ EXJADE® must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. ♦ EXJADE® tablets to be dispersed in water or apple or orange juice. Any residue is to be re-suspended in water or juice and swallowed. Tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion respectively. It is not recommended in patients with severe hepatic impairment.

Non-transfusion-dependent thalassaemia syndromes. Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients. ♦ **Starting daily dose:** The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight. ♦ **Dose adjustment:** It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes. In patients in whom LIC was not assessed and serum ferritin is ≤2,000 µg/l, dosing should not exceed 10 mg/kg. For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 µg/l. ♦ **Treatment cessation:** Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/l), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended. ♦ **Paediatric patients:** In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤800 µg/l. Before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

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

WARNINGS/PRECAUTIONS: ♦ This medicinal product is subject to additional monitoring. ♦ There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with Exjade. ♦ Caution in elderly patients due to a higher frequency of adverse reactions. ♦ EXJADE® has not been studied in patients with renal and hepatic impairment and should be used

EXJADE deferasirox

with caution in such patients. ♦ Due to chances of metabolic acidiosis, in patients where acid-base imbalance is a known complication like diarrhea, renal impairment or renal tubulopathy (Fanconi's syndrome), acid-base balance should be monitored ♦Creatinine clearance, serum creatinine and proteinuria should be monitored weekly in first month after initiation or modification of therapy with EXJADE® and monthly thereafter: dose reduction may be needed in some cases of non-progressive increase in serum creatinine. More frequent creatinine monitoring recommended in patients with an increased risk of renal complications. Dose may be reduced if it is seen in two consecutive visits that serum creatinine rises by >33% above the average of the pre-treatment measurements in adults (and above the age-appropriate upper limit of normal in paediatric patients) and estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min). EXJADE® should be interrupted if serum creatinine shows a progressive rise beyond the age-appropriate upper limit of normal. Rare reports of acute renal failure, some of which required dialysis. Reports of renal tubulopathy mainly in children and adoloscents with betathalassaemia and serum ferritin levels <1,500 microgram/L. Caution in patients who are receiving medicinal products that depress renal function and those receiving high doses of EXJADE® and/or low rates of transfusion. ♦ Monthly monitoring of serum ferritin is recommended to assess patient's response to therapy. ♦ Postmarketing cases of hepatic failure have been reported. Monitoring of serum transaminases, bilirubin and alkaline phosphatase: before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. EXJADE® should be interrupted if persistent and progressive unattributable increase in serum transaminases levels. Not recommended in patients with severe hepatic impairment. ♦ Maintain adequate hydration in patients who develop diarrhoea or vomiting. ♦ Not recommended in patients with short life expectancy (e.g. high risk myelodysplastic syndrome) especially when co-morbidities could increase the risk of adverse events. ♦ Monitor cardiac function in patients with severe iron overload during long term treatment with EXJADE®. ♦ As a general precaution, in paediatric patients with transfusional iron overload, monitor body weight, height and sexual development. ♦ Gastrointestinal irritation may occur. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. There have been rare reports of fatal GI haemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 x 10^9/L. ♦ Skin rashes: EXJADE® should be interrupted if severe rash develops. ♦ Discontinue if severe hypersensitivity reaction occurs. ♦ Recommended ophthalmological/audiological testing before start of treatment and annually. ♦ In patients who develop unexplained cytopenia consider interruption of treatment. ♦ Should not be used during pregnancy unless clearly necessary.♦ Not recommended when breast-feeding. ♦ Caution when driving or operating machinery.♦ Product contains lactose. ♦ Exjade may decrease the efficacy of hormonal contraceptives.

INTERACTIONS: ♦ Should not be taken with aluminium-containing antacids or with other iron chelator therapies. ♦Caution when combined with drugs metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, bepridil, ergotamine, hormonal contraceptive agents). ♦Increases in the dose of EXJADE® should be considered when concomitantly used with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, ritonavir). ♦Concomitant use with repaglinide should be avoided. If combination is necessary, careful monitoring of glucose levels should be performed. An interaction between EXJADE® and other CYP2C8 substrates like paclitaxel cannot be excluded. ♦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:** headache, proteinuria, transaminases increased, rash, pruritus, diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia ♦ **Uncommon:** anxiety, sleep disorder, dizziness, early cataract, maculopathy, hearing loss, pharyngolaryngeal pain, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, pyrexia, oedema, fatigue, renal tubulopathy (acquired Fanconi's syndrome), glycosuria ♦ **Rare:** oesophagitis, optic neuritis ♦ Not known: metabolic acidosis, neutropenia, gastrointestinal perforation, nephrolithiasis, renal tubular necrosis**,** anaemia aggravated,pancytopenia, thrombocytopenia, hypersensitivity reactions (including anaphylaxis and angioedema), acute renal failure, Stevens-Johnson syndrome leukocytoclastic vasculitis, urticaria, erythema multiforme, alopecia, hepatic failure, tubulointerstitial nephritis

LEGAL CATEGORY: POM

PACK SIZES: Packs of 28 dispersible tablets

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

MARKETING AUHORISATION NUMBER: EU/1/06/356/003 and 005

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

2014-MT-EXJ-19-Sept-2014

EXJADE
deferasirox

Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

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

NOVARTIS ONCOLOGY

EXJADE® deferasirox

Novartis Pharma AG
CH-4002 Basel Switzerland

EXJ PB1 09/14 MT