**PRESCRIBING INFORMATION**
**EXJADE® ▼ (deferasirox)**
**90, 180 and 360 mg film coated tablets**

Before prescribing EXJADE, please refer to the Summary of Product Characteristics (SPC). **Presentation:** Blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 90, 180 or 360 on the other). **Indications:** 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.
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. 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. **Posology and method of administration:** For oral use. To be swallowed whole with water. The tablets may be crushed and administered by sprinkling the full dose onto soft food. The dose should be immediately and completely consumed. The 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. *Transfusional iron overload:* EXJADE should be initiated and maintained by experienced specialist physicians. The recommended initial daily dose 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 EXJADE that is numerically one third that of the deferoxamine dose could be considered. 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*:* Serum ferritin should be monitored every month and the dose of EXJADE 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, 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. For detailed dosing recommendations, please refer to the full SPC. *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 overchelation in all patients. The recommended initial daily dose 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. 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 re-accumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended. *Special populations*: Elderly patients: The dosing recommendations for elderly patients are the same as described above. Paediatric population: The dosing recommendations for paediatric 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 patients response to therapy and to minimise the risk of overchelation. 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. In paediatric patients with n*on-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 3 months when serum ferritin is ≤800µg/l. The safety and efficacy of EXJADE in children from birth to 23 months of age have not been established. *Patients with renal impairment:* EXJADE 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:* EXJADE 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%, and 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. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Combination with other iron chelator therapies. Use in patients with estimated creatinine clearance <60 ml/min. **Warnings and Precautions: Renal function:** EXJADE has been studied only in patients with baseline serum creatinine within the age appropriate normal range. During clinical studies, 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. It is recommended that serum creatinine be assessed in duplicate before initiating therapy. Serum creatinine, creatinine clearance (estimated with Cockcroft- Gault or MDRD 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 (including switch of formulation) and monthly thereafter. Dose reduction may be required in some cases where rises in serum creatinine occur. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration if diarrhoea or vomiting develop. Tests for proteinuria should be performed prior to therapy and monthly thereafter. A reduction or interruption in dosing may be considered if indicated by abnormalities in markers of renal tubular function (e.g. glycosuria in non-diabetics, low levels of serum potassium) and/or clinically indicated. There have been post-marketing reports of metabolic acidosis occurring during treatment with EXJADE. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis. Post-marketing cases of severe forms of renal tubulopathy (such as Fanconi syndrome) and renal failure associated with changes in consciousness in the context of hyperammonaemic encephalopathy have been reported in patients treated with deferasirox, mainly in children. Hyperammonaemic encephalopathy should be considered and ammonia levels measured in patients who develop unexplained changes in mental status while on EXJADE therapy. **Hepatic function:** Liver function test elevations have been observed in patients treated with EXJADE. Post-marketing cases of hepatic failure, some of which were fatal, have been reported in patients treated with EXJADE. Care should be taken to maintain adequate hydration in patients who experience volume-depleting events (such as diarrhoea or vomiting), particularly in children with acute illness. Most reports of hepatic failure involved patients with significant morbidities including pre-existing chronic liver conditions (mainly liver cirrhosis) and multi-organ failure. However, the role of EXJADE as a contributing or aggravating factor cannot be excluded. 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, EXJADE should be interrupted. EXJADE is not recommended in patients with a short life expectancy, especially when co-morbidities could increase the risk of adverse events. Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular diarrhoea). **Gastrointestinal disorders:** Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Multiple ulcers have been observed in some patients. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and in case of gastrointestinal ulceration or haemorrhage, Exjade should be discontinued and additional evaluation and treatment promptly initiated. Caution should be exercised in patients who are taking EXJADE 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$^3$ (50x 10$^9$/l). **Skin disorders:** Skin rashes may appear during EXJADE treatment. Interruption of treatment may be necessary. In severe cases a short period of oral steroid administration may be necessary. Severe cutaneous adverse reactions (SCARs) including Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms, have been reported. If severe skin reactions are suspected, EXJADE should be discontinued immediately and should not be reintroduced. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. **Hypersensitivity reactions:** 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. EXJADE should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock. **Vision and hearing:** Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported. Auditory and ophthalmic testing (including fundoscopy) 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. **Blood disorders:** There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with EXJADE. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia. **Other considerations:** Paediatric patients should be monitored for body weight, height and sexual development prior to therapy and annually. Cardiac function should be monitored in patients with severe iron overload with long-term EXJADE treatment. Dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels are recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. **Interactions with other medications:** Not recommended to take with aluminium containing antacid preparations. The concomitant administration of EXJADE with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity. The concomitant administration of EXJADE with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when EXJADE is combined with these substances. Concomitant use with potent UGT inducers may result in a decrease in EXJADE efficacy. Caution should be exercised when combined with substances metabolised through CYP3A4 due to a possible decrease in their efficacy. The concomitant use of EXJADE with repaglinide (a CYP2C8 substrate) should be avoided. The concomitant use with CYP1A2 substrates that have a narrow therapeutic index, such as theophylline, clozapine or tizanidine, is not recommended. Cholestyramine significantly reduced the EXJADE exposure in a mechanistic study to determine the degree of enterohepatic recycling. Concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC). If possible, evaluation of the pharmacokinetics (AUC, clearance) of a busulfan test dose should be performed to allow dose adjustment. **Other important information:** EXJADE is not recommended during pregnancy unless clearly necessary and is also not recommended when breastfeeding. EXJADE may decrease the efficacy of hormonal contraceptives. Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using EXJADE. No fertility data is available for humans. EXJADE has minor influence on the ability to drive and use machines. Early signs of acute overdose may include abdominal pain, diarrhoea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment. Standard procedures for management of overdose may be indicated as well as symptomatic treatment. **Undesirable effects:** *Very Common (≥1/10)*: Blood creatinine increased. *Common (≥1/100 to <1/10)*: Headache, diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, transaminases increased, rash, pruritus, and proteinuria. *Uncommon (≥1/1,000 to <1/100)*: Anxiety, sleep disorder, dizziness, cataract, maculopathy, deafness, laryngeal pain, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder (acquired Fanconi syndrome), glycosuria, pyrexia, oedema, and fatigue. *Rare (≥1/10,000 to <1/1,000)*: Optic neuritis, oesophagitis, and drug reaction with eosinophilia and systemic symptoms. *Not Known (cannot be estimated from available data)*: 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, acute renal failure, tubulointerstitial nephritis, nephrolithiasis, and renal tubular necrosis. For further details on undesirable effects, please refer to the full SPC.
**Legal Category:** POM **Marketing Authorisation (MA) Number and list price:** EU/1/06/356/011 - 90 mg film coated tablets 30 pack, £126.00. EU/1/06/356/014 - 180 mg film coated tablets 30 pack, £252.00. EU/1/06/356/017 - 360 mg film coated tablets 30 pack, £504.00
Full prescribing information is available from Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Tel: 01276 692255.
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**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis uk.patientsafety@novartis.com or online through the patient safety information tool (PSI) at https://psi.novartis.com.**

**If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com**