Understanding EXJADE® (deferasirox) Film-Coated Tablets

A physician guide to dosing and administration

Indications

EXJADE® (deferasirox) film-coated tablets (FCT) 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 FCT 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

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

A New Formulation

EXJADE FCT contains the same active ingredient as EXJADE® (deferasirox) dispersible tablets for oral suspension. This formulation was developed to provide patients with a simplified medication administration process.

When Should EXJADE FCT Treatment Be Initiated?

- It is recommended that EXJADE FCT be started when one or both of the following occurs:
  - After the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells
  - When there is evidence from clinical monitoring that chronic iron overload is present (eg, serum ferritin >1000 mcg/L)

Prior to starting a new patient on EXJADE FCT, obtain:

- Serum ferritin level
- Serum creatinine and creatinine clearance (monitored in duplicate)
- Serum transaminases (AST, ALT), bilirubin, and alkaline phosphatase
- Proteinuria
- Hearing and vision examinations

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Transfusion-Dependent Iron Overload

EXJADE® (deferasirox) film-coated tablets

Starting dose	14 mg/kg/d
Alternate starting doses	7 mg/kg/d*
	21 mg/kg/d†
Dose adjustment increments	3.5-7 mg/kg
Maximum dose	28 mg/kg/d
Dosage strengths	90 mg, 180 mg, 360 mg

Additional dosing considerations presented on the following pages.

* Starting dose of 7 mg/kg/d may be considered for patients receiving <7 mL/kg/mo of packed red blood cells and for whom the objective is maintenance of the body iron level.

† Starting dose of 21 mg/kg/d may be considered for patients receiving >14 mL/kg/mo of packed red blood cells and for whom the objective is reduction of iron overload.

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Administering EXJADE FCT

The administration process of EXJADE FCT is simple and convenient.
EXJADE FCT is a blue, film-coated tablet that has 2 administration options:

1) Swallow the tablet whole with a glass of water

2) Crush the tablet and sprinkle it on a soft food, such as applesauce (apple puree). The dose should be immediately and completely consumed, and not stored for future use

EXJADE FCT should be taken once a day, preferably at the same time each day, and can be taken on an empty stomach or with a light meal.

Considerations for EXJADE FCT Dose Adjustments and Discontinuation

EXJADE FCT is available in 90-, 180-, and 360-mg dosage strengths. Make dose adjustments in steps of 3.5 to 7 mg/kg, if necessary, every 3 to 6 months, and tailor adjustments to the individual patient's response and therapeutic goals.

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE FCT be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin.

For pediatric patients, changes in weight of patients over time must be taken into account when calculating the dose.

BASELINE RENAL IMPAIRMENT	Creatinine clearance <60 mL/min ▶ EXJADE FCT is contraindicated
RENAL IMPAIRMENT DURING THERAPY	Adult patient nonprogressive increases in serum creatinine by 33% above the average of the pretreatment measurements is seen at 2 consecutive visits and cannot be attributed to other causes ▶ Reduce EXJADE FCT dose by 7 mg/kg Pediatric patient increases in serum creatinine above the age-appropriate upper limit of normal at 2 consecutive visits ▶ Reduce EXJADE FCT dose by 7 mg/kg Progressive increase in serum creatinine beyond the upper limit of normal ▶ Interrupt EXJADE FCT. Therapy may be reinitiated depending on individual circumstances

Considerations for EXJADE FCT Dose Adjustments and Discontinuation (cont)

HEPATIC IMPAIRMENT

Moderate (Child-Pugh B) hepatic impairment ▶ Reduce the starting dose by 50%

Severe (Child-Pugh C) hepatic impairment ▶ EXJADE FCT should not be used

Persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes ▶ Interrupt EXJADE FCT. Once the cause of liver function abnormalities has been clarified or after return to normal levels, EXJADE FCT reinitiation may be considered at a lower dose with gradual dose escalation

Other toxicities may require dose adjustment or discontinuation. Monitor patients for thrombocytopenia, worsening anemia, neutropenia, bleeding, vision, and hearing disturbances.

Two Patient Examples

A: Dr Ramos prescribed 270 mg of EXJADE FCT daily.

How was this dose calculated?

Patient's weight: 18 kg

- ▶ Receives 12 mL/kg/mo of packed red blood cells
- ▶ Serum ferritin >1000 mcg/L
- ▶ No renal or hepatic impairment

Formula: 18 kg x 14 mg/kg = 252 mg

Dosage: 270 mg = 180 mg + 90 mg tablet rounded to nearest whole tablet

B: Dr Brandt changed dose of EXJADE FCT from 1170 mg to 540 mg daily.

How was this dose calculated?

Patient's weight: 81 kg

- ▶ Receives 10 mL/kg/mo of packed red blood cells
- ▶ Serum ferritin >1000 mcg/L
- ▶ Creatinine level average prior to start of therapy: 0.9 mg/dL
- ▶ Creatinine level after 3 months on therapy: 1.2 mg/dL (nonprogressive increase seen at 2 consecutive visits)
- ▶ Starting dose of 14 mg/kg reduced by 7 mg/kg

Formula: 81 kg x 7 mg/kg = 567 mg
1170 mg (starting dose) – 567 mg = 603 mg

Dosage: 630 mg = 360 mg + 180 mg + 90 mg tablet rounded to nearest whole tablet

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EXJADE FCT Indications and Important Safety Information

Important note: Before prescribing, consult full prescribing information.

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

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-thalassemia major aged 6 years and older. ◆ 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 other anemias aged 2 years and older; 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. ◆ 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.

Dosage: Transfusional iron overload ◆ Recommended initial daily dose is 14 mg/kg body weight; consider 21 mg/kg for patients receiving >14 ml/kg/month of packed red blood cells (>4 units/month), and for whom the objective is reduction of iron overload; consider 7 mg/kg for patients receiving <7 ml/kg/month of packed red blood cells (<2 units/month), 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 film-coated tablets that is numerically one third that of the deferoxamine dose. For patients who are currently on chelation therapy with the dispersible tablet and switching to the film-coated tablet, the dose should be 30% lower, rounded to the nearest whole tablet. ◆ The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the tablets may be crushed and administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree). The dose should be immediately and completely consumed, and not stored for future use. ◆ EXJADE 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. ◆ **Monthly monitoring of serum ferritin** to assess patient's response to therapy. ◆ Dose to be adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 3.5 to 7 mg/kg. ◆ **Maximum daily dose** is 28 mg/kg body weight. ◆ In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 micrograms/l), consider dose reductions in steps of 3.5 to 7 mg/kg to maintain serum ferritin levels within the target range. ◆ Interrupt treatment if serum ferritin falls consistently below 500 micrograms/l.

Dosage: Non–transfusion-dependent thalassemia syndromes and iron overload ◆ Recommended initial daily dose is 7 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 micrograms/l. In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation. For patients who are currently on chelation therapy with the dispersible tablet and switching to the film-coated tablet, the dose should be 30% lower, rounded to the nearest whole tablet. ◆ **Monthly monitoring of serum ferritin** ◆ Dose adjustment should be considered every 3 to 6 months in steps of 3.5 to 7 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently>2,000 micrograms/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 micrograms/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. ◆ **Maximum daily dose** is 14 mg/kg body weight. ◆ In **pediatric patients** the dosing should not exceed 7 mg/kg; 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 ≤800 micrograms/l.

Dosage: Special population ◆ In moderate hepatic impairment (Child-Pugh B) dose should not exceed 50% of the normal dose. Should not be used in severe hepatic impairment (Child-Pugh C).

Contraindications: Hypersensitivity to deferasirox or to any of the excipients. ◆ Combination with other iron chelator therapies. ◆ Estimated creatinine clearance <60 ml/min.

Warnings and precautions: ◆ Renal Function: Assess serum creatinine in duplicate before initiating therapy; monitor serum creatinine, creatinine clearance and/or plasma cystatin C levels prior to therapy, weekly in the first month after initiation or modification of therapy (including switch of formulation), and monthly thereafter. Dose reduction or interruption may be required in some cases where rises in serum creatinine occur. Postmarketing cases of renal failure (some requiring dialysis) have been reported. There have been reports of renal tubulopathy, **with cases of metabolic acidosis** mainly in children and adolescents with beta-thalassemia. Tests for proteinuria should be performed monthly. Refer the patient to a renal specialist and consider further specialized investigations (such as renal biopsy) if serum creatinine remains significantly elevated and another marker of renal function is also persistently abnormal. **◆ Hepatic Function: Monitor serum transaminases, bilirubin and alkaline phosphatase before the initiation of treatment, every 2 weeks during**

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EXJADE FCT Indications and Important Safety Information (cont)

the first month and monthly thereafter. Interrupt treatment if persistent and progressive unattributable increase in serum transaminase levels occur. Postmarketing cases of hepatic failure (sometimes fatal) have been reported. Not recommended in patients with severe hepatic impairment (Child-Pugh C). ◆ Caution in elderly patients due to a higher frequency of adverse reactions. **Not recommended in patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes) especially when co-morbidities could increase the risk of adverse events.** ◆ Gastrointestinal irritation may occur. Upper gastrointestinal ulceration and hemorrhage, including ulcers complicated with digestive perforation, have been reported in patients, including children and adolescents. There have been reports of fatal gastrointestinal hemorrhages, especially in elderly patients who had hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 • 10^9/l and in patients taking anticoagulants or other drugs with known ulcerogenic potential. Acute pancreatitis has been reported, particularly in children and adolescents. ◆ Interrupt treatment if severe skin rash develops. ◆ Consider reintroduction at a lower dose followed by dose escalation. ◆ Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported. If any SCAR is suspected, EXJADE film-coated tablets should be discontinued immediately and not reintroduced. ◆ Discontinue if severe hypersensitivity reaction occurs. ◆ Annual ophthalmological/audiological testing. ◆ Annual monitoring for body weight, height and sexual development in pediatric patients. ◆ Interruption of treatment should be considered in patients who develop unexplained cytopenia. ◆ Cardiac function should be monitored in patients with severe iron overload during long-term EXJADE film-coated tablets treatment. ◆ Should not be used during pregnancy unless clearly necessary. If used, additional or alternative non-hormonal contraception is recommended. ◆ Not recommended when breastfeeding.

Interactions: Must not be combined with other iron chelator therapies. ◆ Should not be taken with aluminum-containing antacids. ◆ Caution when combined with drugs metabolized through CYP3A4 (e.g. cyclosporine, simvastatin, hormonal contraceptive agents, bepridil, ergotamine). ◆ Concomitant use with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir, cholesteramine) may result in a decrease in EXJADE film-coated tablets efficacy. ◆ Careful monitoring of glucose levels should be performed when repaglinide (a CYP2C8 substrate) and EXJADE film-coated tablets are used concomitantly. EXJADE film-coated tablets may also increase levels of other CYP2C8 substrates like paclitaxel. ◆ 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:* Headache, diarrhea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, transaminases increased, rash, pruritus, proteinuria. ◆ *Uncommon:* Anxiety, sleep disorder, dizziness, cataract, maculopathy, deafness, laryngeal pain, gastrointestinal hemorrhage, gastric ulcer, duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubulopathy disorder (acquired Fanconi syndrome), glycosuria, pyrexia, edema, fatigue. ◆ *Rare:* Esophagitis, optic neuritis, drug reaction with eosinophilia and systemic symptoms (DRESS). ◆ *Not known (cannot be estimated from data):* Stevens-Johnson syndrome, pancytopenia, thrombocytopenia, neutropenia, aggravated anemia, hypersensitivity reactions (including anaphylaxis reactions and angioedema), metabolic acidosis, gastrointestinal perforation, acute pancreatitis, hepatic failure, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, nephrolithiasis, renal tubular necrosis. ◆ Refer to the SmPC for a full list of adverse reactions.

Legal Category: country specific

Packs: country specific information

Reference

EXJADE® dispersible tablets and film-coated tablets [Summary of Product Characteristics]. Novartis; August 2017.

NOVARTIS

EXJADE® (deferasirox) FILM-COATED TABLETS

Novartis Pharma AG
CH-4002 Basel Switzerland