

Drug Regulatory Affairs

EXJADE[®]

(deferasirox)

(in some countries marketed as ASUNRA[®])

125 mg, 250 mg, 500 mg dispersible tablets
(locally available strengths may differ)

Core Data Sheet

Version 1.2

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosing, pharmacovigilance and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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Table of contents

1	Trade name	3
2	Description and composition	3
3	Indication	3
4	Dosage and Administration	3
5	Contraindications	5
6	Warnings and Precautions	5
7	Adverse drug reactions	9
8	Interactions	11
9	Pregnancy and Breast-feeding	12
10	Overdosage	13
11	Clinical pharmacological	13
12	Clinical studies	15
13	Non-clinical safety data	17
14	Pharmaceutical information	18

1 Trade name

EXJADE® 125 mg, 250 mg, 500 mg dispersible tablets.

2 Description and composition

Pharmaceutical form(s)

Dispersible tablets.

Active substance(s)

Each dispersible tablet contains 125 mg / 250 mg / 500 mg deferasirox as active substance.

Excipients

Lactose monohydrate; Crospovidone; Microcrystalline cellulose; Povidone (K30); Sodium lauryl sulphate; Silicon dioxide; Magnesium stearate

3 Indication

EXJADE is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adult and paediatric patients (aged 2 years and over) [1,2,3,4].

4 Dosage and Administration

Dosage

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

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

General target population:

Starting dose

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

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

An initial daily dose of 10 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult), and for whom the objective is maintenance of the body iron level [2,3,4,38].

For patients already well-managed on treatment with deferoxamine, a starting dose of EXJADE that is numerically half that of the deferoxamine dose could be considered (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 20 mg/kg/day of EXJADE) [2,4,18,38].

Maintenance dose

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered [50]. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level [50].

In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range [51]. If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of EXJADE may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated [47,49] (see section 6 Warnings and Precautions).

Special populations: Patients with renal impairment

EXJADE treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections [61]. The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 10 mg/kg (see section 6 Warnings and Precautions).

Patients with hepatic impairment

EXJADE has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as described above. Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter [51] (see section 6 Warnings and Precautions).

Paediatric patients

The dosing recommendations for paediatric patients are the same as for adult patients [2,3]. Changes in weight of paediatric patients over time must be taken into account when calculating the dose.

Elderly patients

The dosing recommendations for elderly patients are the same as described above [3]. In clinical trials, elderly patients experienced a higher frequency of adverse reactions than younger patients and should be monitored closely for adverse reactions that may require a dose adjustment [62].

Method of administration

EXJADE must be taken once daily on an empty stomach at least 30 minutes before food [6,7], preferably at the same time each day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained [8]. After the suspension has been swallowed, any residue must be resuspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

5 Contraindications

Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal [61].

High risk myelodysplastic syndrome (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 [63].

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

6 Warnings and Precautions

The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy (see section 4 Dosage and Administration).

Caution should be used in elderly patients due to a higher frequency of adverse reactions [62].

Renal

Non-progressive rises in serum creatinine have been noted in patients treated with EXJADE, usually within the normal range [2,3]. Cases of acute renal failure have been reported following the post-marketing use of EXJADE [40] (see section 7 Adverse Drug Reactions). There have been rare cases of acute renal failure requiring dialysis [53].

It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy and monitored monthly thereafter.

Patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function may be more at risk of complications and weekly monitoring of serum creatinine and/or creatinine clearance is recommended in the first month after initiation or modification of therapy, and monthly thereafter [39]. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections [61].

Renal tubulopathy has been reported in patients treated with EXJADE [54]. The majority of these patients were children and adolescents with beta-thalassaemia and serum ferritin levels <1,500 microgram/L.

Tests for proteinuria should be performed monthly [39].

Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting [39].

For adult patients, the daily dose of EXJADE may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section 4 Dosage and Administration). For paediatric patients, the dose may be reduced by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, EXJADE should be interrupted. Therapy with EXJADE may be reinitiated depending on the individual clinical circumstances.

Hepatic

Exjade has not been studied in patients with hepatic impairment. EXJADE treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox were not influenced by such transaminase levels. Deferasirox is principally eliminated by glucuronidation and is minimally (about 8%) metabolised by oxidative cytochrome P450 enzymes [9] (see section 11 Clinical Pharmacology).

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials. There have been postmarketing reports of hepatic failure in patients treated with EXJADE. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients (see section 7 Adverse Drug Reactions) [45]. It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter [51]. If there is a persistent and progressive increase in serum transaminase levels that can not be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of EXJADE treatment at a lower dose followed by gradual dose escalation may be considered [2,3,4].

Blood disorders

There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with EXJADE. Most of these patients had preexisting haematologic disorders that are frequently associated with bone marrow failure (see section 7 Adverse Drug Reactions). The relationship of these episodes to treatment with EXJADE is uncertain. In line with the standard clinical management of such haematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with EXJADE should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with EXJADE may be considered, once the cause of the cytopenia has been elucidated [41].

Gastrointestinal

Gastrointestinal irritation may occur during EXJADE treatment. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving EXJADE. There have been rare reports of fatal GI haemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts [62]. Multiple ulcers have been observed in some patients (see section 7 Adverse Drug Reactions) [48]. Physicians and patients should remain alert for signs and symptoms of GI ulceration and haemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected.

Caution should be exercised in patients who are taking EXJADE in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see section 8 Interactions), and in patients with platelet counts $<50 \times 10^9/L$ [48,62].

Hypersensitivity reactions

Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving EXJADE, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 7 Adverse Drug Reactions). If reactions are severe, EXJADE should be discontinued and appropriate medical intervention instituted [42].

Skin disorders

Skin rashes may appear during EXJADE treatment. For rashes of mild to moderate severity, EXJADE may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, EXJADE may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction may be conducted in combination with a short period of oral steroid administration [2,3,4]. Rare cases of erythema multiforme have been reported during EXJADE treatment [55].

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with EXJADE treatment (see section 7 Adverse Drug Reactions). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of EXJADE treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered [2,3,4].

Other considerations

It is recommended that serum ferritin be measured every month in order to assess the patient's response to therapy (see section 4 Dosage and Administration). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range [51]. If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of EXJADE may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated [47,49].

EXJADE has not been associated with growth retardation in children followed for up to 5 years in clinical trials [1,2,3,4,56,57,64]. However, as a general precautionary measure, body weight and longitudinal growth in paediatric patients can be monitored at regular intervals (every 12 months).

EXJADE must not be combined with other iron chelator therapies as the safety of such combinations has not been established.

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

Driving and using machines

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

7 Adverse drug reactions

Summary of the safety profile

The most frequent reactions reported during chronic treatment with EXJADE in adult and paediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea, or abdominal pain), and skin rash in about 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients [44]. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see section 6 Warnings and Precautions).

Elevations of liver transaminases were reported in about 2% of patients. These were not dependent on dose and most of these patients had elevated levels prior to receiving EXJADE. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). There have been postmarketing reports of hepatic failure in patients treated with EXJADE. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients [45].

As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with EXJADE (see section 6 Warnings and Precautions).

The following adverse drug reactions, listed in Table 1, have been reported in clinical studies following treatment with EXJADE. Adverse reactions [16] are ranked below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated summary of adverse drug reactions from clinical trials**Table 1 Adverse drug reactions reported in clinical studies**

Psychiatric disorders	
Uncommon:	anxiety, sleep disorder
Nervous system disorders	
Common:	headache
Uncommon:	dizziness
Eye disorders	
Uncommon:	early cataract, maculopathy
Rare:	optic neuritis [49]
Ear and labyrinth disorders	
Uncommon:	hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	gastrointestinal haemorrhage [48], gastric ulcer (including multiple ulcers) [48], duodenal ulcer [48], gastritis
Rare:	oesophagitis [48]
Hepatobiliary disorders	
Common:	transaminases increased
Uncommon:	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritus
Uncommon:	pigmentation disorder
Rare:	erythema multiforme [55]
Renal and urinary disorders	
Very common:	blood creatinine increased
Common:	proteinuria
Uncommon:	renal tubulopathy (Fanconi's syndrome) [47]
General disorders and administration site conditions	
Uncommon:	pyrexia, oedema, fatigue

Listing of Adverse drug reactions from post-marketing spontaneous reports

Spontaneously reported adverse reactions, presented in Table 2, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 2 Adverse drug reactions derived from spontaneous reports

Renal and urinary disorders acute renal failure (mostly serum creatinine increases $\geq 2x$ upper limit of normal, and usually reversible after treatment interruption) [40]
Hepatobiliary disorders hepatic failure [45]
Skin and subcutaneous tissue disorders leukocytoclastic vasculitis [43], urticaria [42], alopecia [58]
Immune system disorders hypersensitivity reactions (including anaphylaxis and angioedema) [39]

There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia and thrombocytopenia in patients treated with EXJADE. Most of these patients had preexisting haematologic disorders that are frequently associated with bone marrow failure (see section 6 Warnings and Precautions). The relationship of these episodes to treatment with EXJADE is uncertain [41].

Paediatric population

Renal tubulopathy has been reported in patients treated with EXJADE [54]. The majority of these patients were children and adolescents with beta -thalassaemia and serum ferritin levels $<1,500$ microgram/L.

8 Interactions

Agents that may decrease EXJADE systemic exposure

In a healthy volunteer study, the concomitant administration of EXJADE (single dose of 30 mg/kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%) [52]. Therefore, the concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. If EXJADE and a potent UGT inducer are used concomitantly, increases in the dose of EXJADE should be considered based on clinical response to therapy.

Interaction with food

The bioavailability of deferasirox was increased to a variable extent when taken along with food [6,7,11]. EXJADE must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see section 4 Dosage and Administration).

Interaction with midazolam and other agents metabolized by CYP3A4

In a healthy volunteer study, the concomitant administration of EXJADE and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% to 26%). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with

substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents) [46].

Interaction with repaglinide and other agents metabolized by CYP2C8

In a healthy volunteer study, the concomitant administration of EXJADE (repeated dose of 30 mg/kg/day) and the CYP2C8 substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide AUC and C_{max} by 131% (90% CI: 103% to 164%) and 62% (90% CI: 42% to 84%), respectively [52]. When EXJADE and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between EXJADE and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolized by CYP1A2

In a healthy volunteer study, the concomitant administration of EXJADE (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing [65]. When EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between EXJADE and other CYP1A2 substrates may be possible.

Other Information

No interaction was observed between EXJADE and digoxin in healthy volunteers [13].

The concomitant administration of EXJADE and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences.

Anticipated interactions resulting in a concomitant use not recommended

The concomitant administration of EXJADE and aluminium-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron [10], EXJADE tablets must not be taken with aluminium-containing antacid preparations.

Concomitant administration of EXJADE with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of EXJADE in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see section 6 Warnings and Precautions) [48].

9 Pregnancy and Breast-feeding

Pregnancy

No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see section 13 Non-clinical Safety Data). The potential risk for humans is unknown.

As a precaution, it is recommended that EXJADE not be used during pregnancy unless clearly necessary.

Breast-feeding

In animal studies, deferasirox was found to be rapidly and extensively secreted into maternal milk [14]. No effect on the offspring was noted [15]. It is not known if deferasirox is secreted into human milk. Breast-feeding while taking EXJADE is not recommended.

10 Overdosage

Cases of overdose (2 to 3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved without long-term consequences after a dose interruption [39]. Single doses of 80 mg/kg in iron overloaded thalassaemic patients have been tolerated, with only mild nausea and diarrhoea noted [17]. Single doses up to 40 mg/kg in normal subjects have been well tolerated [11].

Acute signs of overdose may include nausea, vomiting, headache, and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment.

11 Clinical pharmacological

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

Mechanism of action

Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals [2,3,4].

Pharmacodynamic properties

In an iron balance metabolic study in iron overloaded adult thalassaemic patients, EXJADE at daily doses of 10, 20 and 40 mg/kg induced the mean net excretion of 0.119, 0.329, and 0.445 mg Fe/kg body weight/day, respectively [5].

EXJADE has been investigated in adult and paediatric patients (aged 2 years and older) with chronic iron overload due to blood transfusions. The underlying conditions requiring transfusion included beta-thalassaemia [2,3,18], sickle cell disease [4], and other congenital and acquired anemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anaemia and other very rare anemias) [3].

Daily treatment with EXJADE at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight) on average, respectively, and serum ferritin was reduced by about -36 and -926 microgram/L on average, respectively [2]. At these same doses the ratios of iron excretion : iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. EXJADE induced similar responses in iron overloaded patients with

other anemias [3,4]. Daily doses of 10 mg/kg for one year could maintain liver iron and serum ferritin levels, and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions (see Section 4 Dosage and Administration) [3,4]. Serum ferritin assessed by monthly monitoring reflected changes in liver iron concentration indicating that trends in serum ferritin can be used to monitor response to therapy.

Clinical data from patients with normal cardiac function at baseline (114 patients with cardiac siderosis and 78 patients without cardiac siderosis) using MRI indicate that treatment with EXJADE for one year reduces levels of iron in the heart (in patients with cardiac siderosis) and may prevent cardiac iron accumulation (in patients without cardiac siderosis) [60].

Pharmacokinetic properties

Absorption

Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours [2,5,18]. The absolute bioavailability (AUC) of deferasirox from EXJADE tablets is about 70% compared to an intravenous dose [8]. Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) [6] and by about 50% when taken along with a standard breakfast [7]. The bioavailability (AUC) of deferasirox was moderately (approx. 13 to 25%) elevated when taken 30 minutes before meals with normal or high fat content [7]. The total exposure (AUC) to deferasirox when taken after dispersion of tablets in orange juice or apple juice was equivalent to the exposure after dispersion in water (relative AUC ratios of 103% and 90%, respectively) [12,38].

Distribution

Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin [19], and has a small volume of distribution of approximately 14 L in adults [8].

Biotransformation

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3 [20]. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%) [9]. No inhibition of deferasirox metabolism by hydroxyurea was observed in vitro [21]. Deferasirox undergoes enterohepatic recycling [59]. In a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

Elimination

Deferasirox and its metabolites are primarily excreted in the faeces (84% of the dose). Renal excretion of deferasirox and its metabolites is minimal (8% of the dose) [9]. The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours [5,18].

Linearity / non-linearity

The C_{\max} and AUC_{0-24h} of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3 [5,18].

Special Populations**Paediatric patients**

The overall exposure of adolescents (12 to ≤ 17 years) and children (2 to < 12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was about 50 % lower than in adults [22,23]. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Gender

Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males [23]. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Elderly patients

The pharmacokinetics of deferasirox have not been studied in elderly patients (aged 65 or older).

Renal or hepatic impairment

The pharmacokinetics of deferasirox have not been studied in patients with renal or hepatic impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range [24].

12 Clinical studies

An open-label, randomized, Phase III, active comparator control study to compare EXJADE and Desferal (deferroxamine) was conducted in patients with beta-thalassemia and transfusional hemosiderosis [2]. Patients ≥ 2 years of age were randomized in a 1:1 ratio to receive either oral EXJADE at starting doses of 5, 10, 20 or 30 mg/kg once daily or subcutaneous Desferal (deferroxamine) at starting doses of 20 to 60 mg/kg for at least 5 days per week based on liver iron concentration (LIC) at baseline (2 to 3, >3 to 7, >7 to 14 and >14 mg Fe/g dry weight (dw)). Patients randomized to deferroxamine who had LIC values < 7 mg Fe/g dw were permitted to continue on their prior deferroxamine dose, even though the dose may have been higher than specified in the protocol.

LIC was assessed at baseline and after 12 months of therapy by liver biopsy or non-invasively by biomagnetic susceptometry. Success rate, the primary efficacy endpoint, was defined as a reduction in LIC of ≥ 3 mg Fe/g dw for baseline values ≥ 10 mg Fe/g dw, reduction of baseline values between 7 and < 10 to < 7 mg Fe/g dw, or maintenance or reduction for baseline values

<7 mg Fe/g dw. EXJADE was to be declared non-inferior to deferoxamine if the lower limit of the 95% confidence interval (two-sided) of the difference in success rates was above -15%.

In total, 586 patients were randomized. Demographics were well balanced. Fifty-one percent of the patients were <16 years of age. The overall success rates were 52.9% for EXJADE and 66.4% for deferoxamine with a difference of -13.5 in success rates and a 95% CI of [-21.6, -5.4]. Non-inferiority to deferoxamine was not achieved because the lower limit of the CI was below -15%. This is attributed to the imbalance of the protocol-specified dose to the actual dose in the two lowest dose cohorts of the deferoxamine arm (Table 3). However, non-inferiority was demonstrated in a group of patients with baseline LIC levels ≥ 7 mg Fe/g dw who were allocated to the higher dose groups (EXJADE doses of 20 or 30 mg/kg and deferoxamine doses of ≥ 35 mg/kg). The success rates with EXJADE and deferoxamine were 58.6% and 58.9%, respectively, and the lower limit of the 95% CI (-10.2%) was above the non-inferiority threshold of -15%.

In patients with LIC ≥ 7 mg Fe/g dw who were treated with EXJADE 20 to 30 mg/kg per day, a statistically significant reduction in LIC from baseline was observed (-5.3 ± 8.0 mg Fe/g dw, $p < 0.001$, t-test) which was not statistically significantly different from deferoxamine (-4.3 ± 5.8 mg Fe/g dw, $p = 0.367$). Dose dependent effects in serum ferritin and in the ratio of iron excretion/iron intake from EXJADE doses of 5 to 30 mg/kg were also observed (Table 3).

Table 3 Ratio of iron excretion/iron intake and change in serum ferritin levels from baseline to 1 year of treatment in the primary efficacy study

Protocol recommended dose (mg/kg/day)		Mean actual prescribed dose (mg/kg/day)		Ratio of iron excretion / iron intake		Serum ferritin levels ($\mu\text{g/L}$) Mean change from baseline \pm SD	
EXJADE	Defer-oxamine	EXJADE	Defer-oxamine	EXJADE Mean \pm SD (n)	Defer-oxamine Mean \pm SD (n)	EXJADE Mean \pm SD (n)	Defer-oxamine Mean \pm SD (n)
5	20-30	6.2 \pm 1.6	33.9 \pm 9.9	0.58 \pm 0.328 (15)	0.95 \pm 0.101 (13)	+1189 \pm 700 (15)	+211 \pm 459 (13)
10	25-35	10.2 \pm 1.2	36.7 \pm 9.2	0.67 \pm 0.365 (68)	0.98 \pm 0.217 (75)	+833 \pm 817 (73)	+32 \pm 585 (77)
20	35-50	19.4 \pm 1.7	42.4 \pm 6.6	1.02 \pm 0.398 (77)	1.13 \pm 0.241 (87)	-36 \pm 721 (80)	-364 \pm 614 (89)
30	≥ 50	28.2 \pm 3.5	51.6 \pm 5.8	1.67 \pm 0.716 (108)	1.44 \pm 0.596 (98)	-926 \pm 1416 (115)	-1003 \pm 1428 (101)

A second trial, an open-label, non-comparative, Phase II trial of efficacy and safety of EXJADE given for 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine, was also conducted [3]. Patients received 5, 10, 20, or 30 mg/kg per day of EXJADE based on baseline LIC. The primary endpoint was to demonstrate a success rate significantly greater than 50% with EXJADE.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, $n=47$; Diamond-Blackfan syndrome, $n=30$; other, $n=22$). Nineteen percent of patients were <16 years of age and 16% were ≥ 65 . Thirty-seven patients had not received prior chelation

therapy. In the total population, the success rate (50.5%) was not statistically significantly higher than 50%. This was attributed to the fact that the doses of 5 and 10 mg/kg were insufficient for the ongoing rate of iron intake from blood transfusions. However, in patients with LIC ≥ 7 mg Fe/g dw for whom both baseline and end of study LIC was available and who received EXJADE 20 to 30 mg/kg per day, the success rate was 58.5% [$p=0.022$ (50.3, 66.6)] and there was a statistically significant reduction in the absolute LIC from baseline to end of study (-5.5 ± 7.4 mg Fe/g dw, $p < 0.001$, t-test). There was also a dose dependent effect on serum ferritin and the ratio of iron excretion to iron intake from doses of 5 to 30 mg/kg per day.

A third study was conducted in patients with sickle cell disease and transfusional hemosiderosis [4,56]. This study was an open-label, randomized, Phase II study of the safety and efficacy of EXJADE relative to deferoxamine given for 1 year. Patients were randomized to EXJADE at doses of 5, 10, 20, or 30 mg/kg per day or subcutaneous deferoxamine at doses of 20 to 60 mg/kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with EXJADE and 63 with deferoxamine. Forty-four percent of patients were < 16 years of age and 91% were Black. At the end of the study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least one post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving EXJADE ($n=113$) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine ($n=54$).

A cardiac sub-study was conducted as part of a Phase IV study [60]. The cardiac sub-study was a one year, prospective, open-label, single-arm study which included two cohorts of severely iron overloaded beta-thalassemia patients with LVEF values $\geq 56\%$: 114 patients with baseline T2* values > 5 to < 20 ms indicating myocardial siderosis (treatment cohort) and 78 patients with myocardial T2* ≥ 20 ms indicating no clinically significant cardiac iron deposition (prevention cohort). In the treatment cohort, the deferasirox starting dose was 30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. In the prevention cohort, the deferasirox starting dose was 20-30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. The primary endpoint of the cardiac sub-study was the change in T2* at one year. In the treatment cohort, T2* (geometric mean \pm coefficient of variation) significantly increased from a baseline value of 11.2 ms $\pm 40.5\%$ to 12.9 ms $\pm 49.5\%$, representing a significant improvement of 16% ($p < 0.0001$). In the treatment cohort, improvement in T2* was observed in 69.5% of patients and stabilization of T2* in 14.3% of patients. LVEF remained stable and within the normal range: $67.4 \pm 5.7\%$ to $67.1 \pm 6.0\%$. In the prevention cohort, myocardial T2* remained within the normal range and was unchanged from a baseline value of 32.0 ms $\pm 25.6\%$ to 32.5 ms $\pm 25.1\%$ ($+2\%$; $p = 0.565$) indicating that daily treatment with deferasirox can prevent cardiac iron loading in beta-thalassemia patients with a history of high transfusion exposure, and regular, ongoing transfusions.

13 Non-clinical safety data

Preclinical data reveal no special hazard for patients with iron overload, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. The main findings were kidney toxicity [25-29] and lens opacity

(cataracts) [27,30,31]. Similar findings were observed in neonatal and juvenile animals [30]. The kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron [32,33].

The potential for toxicity to reproduction was assessed in rats and rabbits [34,35]. Deferasirox was not teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother [34,36]. Deferasirox did not cause other effects on fertility or reproduction [37].

14 Pharmaceutical information

Incompatibilities

Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

Special Precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture. Shelf life is 3 years. Exjade must be kept out of the reach and sight of children.

Instructions for use and Handling

No special requirements.

This is a non-referenced document.