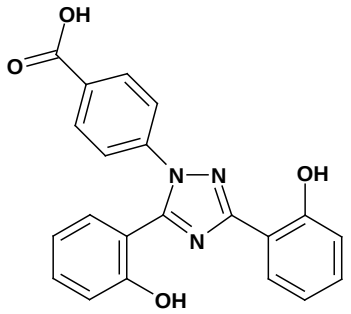
Attachment 1: Product information for AusPAR Product Deferasirox Exjade Novartis PM-2012-03063-1-4 Date of Finalisation 6 March 2014. This Product Information was approved at the time this AusPAR was published.

EXJADE®
(deferasirox)

NAME OF THE MEDICINE

Chemical name: 4-[3,5-Bis-(2-hydroxyphenyl)-[1,2,4]-triazol-1-yl]benzoic acid
Molecular formula: $C_{21}H_{15}N_3O_4$
CAS number: 201530-41-8
Molecular weight: 373.4
Structural formula:



DESCRIPTION

EXJADE® (deferasirox) is an orally active iron chelating agent. EXJADE dispersible tablets for oral suspension contain 125 mg, 250 mg, or 500 mg deferasirox. Deferasirox is a white to slightly yellow powder and is a non-chiral compound. At the physiological pH of the intestine, the solubility is about 40 mg/L.

Excipients: Lactose, crospovidone, povidone, sodium lauryl sulphate, cellulose-microcrystalline, silica-colloidal anhydrous and magnesium stearate.

PHARMACOLOGY

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 very low affinity for zinc and copper and does not cause constant low serum levels of these metals.

Pharmacodynamics

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.

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, sickle cell disease, and other congenital and acquired anaemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anaemia and other very rare anaemias)(see CLINICAL TRIALS).

In patients with non-transfusion-dependent thalassemia syndromes and iron overload, treatment with EXJADE at a dose of 10 mg/kg/day for one year led to a reduction in mean liver iron concentration from baseline by -3.80 mg Fe/g dw, while an increase of 0.38 mg Fe/g dw was observed in patients treated with placebo. In addition, treatment with EXJADE at a dose of 10 mg/kg/day for one year led to a reduction in mean serum ferritin from baseline by -222.0 microgram/L, while an increase of 114.5 microgram/L was observed in patients treated with placebo.

Pharmacokinetics

Absorption:

Deferasirox is rapidly absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from EXJADE tablets is about 70% (90% CI 0.62, 0.80) compared to an intravenous dose. The C_{max} and AUC_{0-24h} of deferasirox increase approximately linearly with dose under steady-state conditions. Upon daily oral dosing exposure increased by an accumulation factor of 1.3 to 2.3.

Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and increased by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approximately 13 to 25%) elevated when taken 30 minutes before meals with normal or high fat content. EXJADE must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see DOSAGE AND ADMINISTRATION).

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).

Distribution:

The *in vitro* binding of deferasirox to albumin (40 g/L) was constant at 98%-99% for deferasirox concentrations between 10 and 105 µg/mL. Binding of deferasirox to α_1-acid glycoprotein (1 g/L) decreased from 85% to 8% with increasing deferasirox concentrations (0.5-105 µg/mL or 1.3-263 µmol/L), indicating saturable binding of this protein. Binding to γ-globulins was negligible. Overall, albumin is the main protein responsible for binding of deferasirox in plasma. Deferasirox has a small volume of distribution of approximately 14 L in adults.

Metabolism:

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. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No inhibition of deferasirox metabolism by hydroxyurea was observed in an *in vitro* study. Deferasirox undergoes enterohepatic recycling. 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). The mean apparent elimination half-life ($t_{1/2}$) after an oral dose ranged from 8 to 16 hours. Following IV administration deferasirox clearance was measured to be 3.53±0.97 L/h.

Pharmacokinetics in special patient groups:

Pharmacokinetics in children:

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 (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics in the elderly:

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

Pharmacokinetic differences with gender:

Females have a moderately lower non-significant apparent clearance (by 17.5%) of deferasirox compared to males. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Pharmacokinetics in patients with impaired renal or hepatic function:

The pharmacokinetics of deferasirox has not been studied in patients with renal impairment. The average AUC of deferasirox in 6 subjects with mild hepatic impairment (Child-Pugh A) increased 16% over that found in 6 subjects with normal hepatic function, while the average AUC of deferasirox in 6 subjects with moderate hepatic impairment (Child-Pugh B) increased 76% over that found in 6 subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment increased 22% over that found in subjects with normal hepatic function. The impact of severe hepatic impairment (Child-Pugh C) was assessed in only one subject (see PRECAUTIONS). The pharmacokinetics of deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

CLINICAL TRIALS

The primary efficacy study, Study 0107, was an open-label, randomised, Phase III, active comparator control study to compare EXJADE and desferrioxamine in patients with β-thalassaemia and transfusional haemosiderosis. Patients ≥2 years of age were randomised 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 (desferrioxamine) at starting doses of 20 to 60 mg/kg for at least 5 days per week based on LIC (liver iron concentration) at baseline (2 to 3, >3 to 7, >7 to 14 and >14 mg Fe/g dw). Patients randomised to desferrioxamine who had LIC values <7 mg Fe/g dw were permitted to continue on their prior desferrioxamine dose, even though the dose may have been higher than specified in the protocol. Consequently, the ratio of EXJADE to desferrioxamine doses for the two lower LIC categories was disproportionately low (1:4) compared to the two upper LIC categories (1:2).

Treatment duration was 12 months. LIC, an accepted indicator of total body iron burden, 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 LIC to below 7 mg Fe/g dw for baseline values ≥ 7 and < 10 mg Fe/g dw, or maintenance or reduction for baseline values < 7 mg Fe/g dw. EXJADE was to be declared non-inferior to desferrioxamine if the lower limit of the 95% confidence interval (two-sided) of the difference in success rates was above -15%.

The primary efficacy population consisted of 553 patients (EXJADE n=276; desferrioxamine n=277) who had LIC evaluated at baseline and 12 months, or who discontinued prior to 12 months due to an AE. Fifty-one percent of the patients were <16 years of age. The overall success rates were 52.9% for EXJADE and 66.4% for desferrioxamine with a difference of -13.5 in success rates and a 95% CI of [-21.6, -5.4]. Non-inferiority to desferrioxamine was not achieved because the lower limit of the CI was below -15%. 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 desferrioxamine doses of ≥ 35 mg/kg). For this group of patients, the success rates with EXJADE and desferrioxamine 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%. This additional analysis was a post-hoc amendment to the protocol prior to database lock.

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). This reduction in LIC was not statistically significantly different from that observed in the desferrioxamine treated patients (-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 1).

Table 1 Ratio of iron excretion/iron intake and change in serum ferritin levels from baseline to 1 year of treatment in the primary efficacy study 0107

Protocol Recommended Dose (mg/kg/day)		Ratio of iron excretion/iron intake		Serum ferritin levels (µg/L) Mean change from baseline ± SD	
EXJADE	**Desferrioxamine**	**EXJADE Mean ± SD (n)**	**Desferrioxamine Mean ± SD (n)**	**EXJADE Mean ± SD (n)**	**Desferrioxamine Mean ± SD (n)**
5	**20-30**	0.58 ± 0.328 (15)	0.95 ± 0.101 (13)	+1189 ± 700 (15)	+211 ± 459 (13)
10	**25-35**	0.67 ± 0.365 (68)	0.98 ± 0.217 (75)	+833 ± 817 (73)	+32 ± 585 (77)
20	**35-50**	1.02 ± 0.398 (77)	1.13 ± 0.241 (87)	-36 ± 721 (80)	-364 ± 614 (89)
30	**≥50**	1.67 ± 0.716 (108)	1.44 ± 0.596 (98)	-926 ± 1416 (115)	-1003 ± 1428 (101)

Desferrioxamine appeared more effective in the 2 to 5 years age group although the difference was not statistically significant. Success rates in this age group were 71.4% (95% CI: 54.7% - 88.2%) with desferrioxamine and 42.9% (95% CI: 24.5 – 61.2) with EXJADE. Reduced efficacy in this age group may have been the result of reduced systemic exposure. For a given mg/kg dose of EXJADE, systemic exposure in children aged 2-5 is approximately 50% lower than in adults (see Pharmacokinetics, Dosage and Administration).

The results of the primary efficacy study are supported by the second major efficacy study, Study 0108, an open-label, non-comparative, phase II trial of efficacy and safety of EXJADE given for 1 year to patients with chronic anaemias and transfusional haemosiderosis unable to be treated with desferrioxamine. Similar to Study 0107, 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 β-thalassaemia and 99 patients with other congenital or acquired anaemias (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%. 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.

In both of these year-long clinical studies, monthly monitoring of serum ferritin was shown to reflect changes in liver iron concentration and thus can be used to monitor response to therapy.

Study 0109 was an open-label, randomised, Phase II, active comparator control study to compare EXJADE and desferrioxamine in patients with sickle cell disease and transfusional hemosiderosis. As in Study 0107, patients received 5, 10, 20, or 30, mg/kg per day of EXJADE or subcutaneous desferrioxamine at doses of 20 to 60 mg/kg for 5 days per week based on baseline LIC. The primary objective of this study was safety and tolerability [see ADVERSE EFFECTS]. A total of 132 patients were treated with EXJADE and 63 patients with desferrioxamine. At the 12 month analysis, dose-dependent increases in the ratio of iron excretion to iron intake from doses of 5 to 30 mg/kg per day of EXJADE were observed.

Study 2209 was a randomized, double-blind, placebo-controlled study to compare EXJADE and placebo was conducted in patients with non-transfusion-dependent thalassemia syndromes and iron overload. Patients ≥10 years of age were enrolled in the study in a 2:1:2:1 randomization to receive either EXJADE 5 mg/kg/day or EXJADE 10 mg/kg/day or matching placebo.

Transfusion independency of the patients was confirmed by the fact that blood transfusions 6 months prior to study start were not allowed and patients were excluded if a regular transfusion program was anticipated during the study. Iron overload was diagnosed by a serum ferritin >300 microgram/L at screening (two consecutive values at least 14 days apart from each other) and LIC ≥5 mg Fe/g dw measured by R2 MRI at screening. All patients with non-transfusion-dependent thalassemia syndromes were allowed with the exception of patients with HbS-variants or those whose clinical condition allowed phlebotomy.

In total, 166 patients were randomized. Demographics were well balanced. The main underlying disease was beta-thalassemia intermedia in 95 (57.2%) patients and HbE beta-thalassemia in 49 (29.5%) patients. The primary efficacy endpoint of change in liver iron concentration (LIC) from baseline to Week 52 was statistically significant in favour of both EXJADE treatment groups compared with placebo (Table 2). Furthermore, a statistically significant dose effect of EXJADE was observed in favour of the 10 mg/kg/day dose.

Table 2 Primary efficacy analysis (Study 2209) – Analysis of covariance of absolute change in liver iron concentration (mg Fe/g dw) between baseline and Week 52 (Full Analysis Set)

	EXJADE 5 mg/kg/day (N=55)	EXJADE 10 mg/kg/day (N=55)	Placebo (N=56)
Change from baseline			
Number of evaluable patients	51	54	54
Least squares mean	-1.95	-3.80	0.38
Standard error	0.500	0.484	0.486
95% confidence interval	-2.94, -0.96	-4.76, -2.85	-0.59, 1.34
Difference of EXJADE - Placebo			
Least squares mean	-2.33	-4.18	-
Standard error	0.700	0.687	-
95% confidence interval (1)	-3.89, -0.76	-5.71, -2.64	-
p-value (2)	0.001	<.001	-
Difference of EXJADE 10 mg/kg - EXJADE 5 mg/kg			
Least squares mean	-	-1.85	-
Standard error	-	0.695	-
95% confidence interval	-	-3.22, -0.48	-
p-value (3)	-	0.009	-

Estimates were obtained from an ANCOVA model for change in LIC between baseline and Week 52 with treatment as factor and baseline LIC as covariate.

(1) two-sided simultaneous confidence intervals using Dunnett's adjustment

(2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in LIC is not greater under EXJADE than under placebo. Critical alpha-level: 0.025

(3) two-sided p-value testing the hypothesis that the change in LIC is identical in the two EXJADE groups. Critical alpha-level: 0.05

The last available post-baseline LIC was carried forward if no LIC value was available at Week 52.

Only patients with both baseline and at least one post-baseline LIC value were included for this analysis.

The primary efficacy result was supported by additional analyses which showed a clear dose-response effect; this was reflected by a greater percentage of patients with an LIC decrease of ≥3 mg Fe/g dw in the 10 mg/kg/day EXJADE group compared to the 5 mg/kg/day EXJADE group (56.4% versus 32.7%, respectively). In addition, a reduction of ≥30% in LIC between baseline and Week 52 was reported in approximately twice as many patients in the 10 mg/kg/day EXJADE group (49.15%) compared to the 5 mg/kg/day EXJADE group (25.5%).

In clinical trials, Exjade has been shown to reduce liver iron concentration and serum ferritin levels. Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed.

INDICATIONS

The treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older. Exjade is also indicated for the treatment of chronic iron overload in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine therapy or in whom desferrioxamine has proven ineffective.

EXJADE is also indicated for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

CONTRAINDICATIONS

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

Platelet counts <50 x 10^9/L.

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.

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

PRECAUTIONS

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

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

In post-marketing experience, there have been reports of serious adverse reactions, some with fatal outcome, in patients taking Exjade therapy, predominantly when the drug was administered to patients with advanced age, complications from underlying conditions, or very advanced disease. Most of these deaths occurred within six months of Exjade initiation, and generally involved worsening of the underlying condition. The reports do not rule out the possibility that Exjade may have contributed to deaths.

Renal disturbances:

Non-progressive rises in serum creatinine have been noted in some patients treated with EXJADE, usually within the normal range (see ADVERSE EFFECTS). Acute renal failure, fatal in some patients and requiring dialysis in others, has been reported following the post-marketing use of Exjade (see ADVERSE EFFECTS). Most fatalities occurred in patients with multiple co-morbidities and who were in advanced stages of their haematological disorders.

It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy, to establish a reliable pre-treatment baseline and monitored monthly thereafter.

Exjade has not been studied in patients with renal impairment and must be used with caution in such patients. 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. Caution should be used in patients with creatinine clearance between 40 and less than 90 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

Renal tubulopathy has been reported in patients treated with EXJADE. 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.

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

Consider dose reductions, interruptions, or discontinuation for increases in serum creatinine. 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. 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 Disturbances:

EXJADE has been studied in a clinical trial in subjects with hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50%. EXJADE should not be used in patients with severe hepatic impairment (Child-Pugh C) (see Clinical pharmacology). 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 (see 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 occurred in patients greater than 55 years of age and in patients with significant comorbidities including liver cirrhosis and multi-organ failure. Fatal outcomes were reported in some of these patients (see ADVERSE EFFECTS). 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. If there is a persistent and progressive increase in serum transaminase levels that cannot 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.

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. Multiple ulcers have been observed in some patients (see ADVERSE EFFECTS). 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 and in patients receiving anticoagulants (see Interactions with Other Medicines).

Skin rash:

Cases of Stevens-Johnson syndrome (SJS) have been reported during the post-marketing period. If SJS is suspected EXJADE should be discontinued.

Rare cases of erythema multiforme have been reported during EXJADE treatment.

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.

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 ADVERSE EFFECTS). If reactions are severe, EXJADE should be discontinued and appropriate medical intervention instituted.

Disturbances of vision and hearing:

Auditory (decreased hearing) and ocular (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) disturbances have been reported with EXJADE treatment (see ADVERSE EFFECTS). Auditory and ophthalmic testing (including slit lamp examination and dilated 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.

Cytopenias:

There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias including agranulocytosis, neutropenia, thrombocytopenia, and pancytopenia in patients treated with EXJADE. Some of these patients died however the relationship of these episodes to treatment with EXJADE is uncertain. Most of these patients had preexisting haematologic disorders that are frequently associated with bone marrow failure (see ADVERSE EFFECTS). 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.

Other precautions:

It is recommended that serum ferritin be measured every month in order to assess the patient's response to therapy (see DOSAGE AND ADMINISTRATION). If serum ferritin falls consistently below 500 µg/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.

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). Patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

Paediatric use:

EXJADE has not been associated with growth retardation in children followed for up to 5 years in clinical trials. However, as a general precautionary measure, body weight and longitudinal growth in paediatric patients can be monitored at regular intervals (every 12 months). In children aged between 2 and 5 years, exposure to deferasirox is lower than in adults. This age group may therefore require higher maintenance doses than adults (see DOSAGE AND ADMINISTRATION).

Use in the elderly

In the elderly, data to support the safety and efficacy of doses greater than 30mg/kg per day are limited. Closely monitor elderly patients for early signs or symptoms of adverse reactions that may require a dose adjustment. Elderly patients are at increased risk for Exjade toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Effects on ability to drive and use machines:

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

Genotoxicity: Deferasirox was not genotoxic in *in vitro* tests for bacterial gene mutation or chromosomal aberrations in human lymphocytes. Positive responses were seen in an *in vitro* (V79) and in rat *in vivo* (bone marrow) micronucleus tests, which may have been related to iron chelation. No response was seen in another rat *in vivo* micronucleus test (liver) with doses that exceeded the maximum tolerated dose.

Carcinogenicity: Deferasirox was not carcinogenic in a 104 week study in rats or in a 26 week study in transgenic p53 +/- heterozygous mice that were maintained on an iron-supplemented diet. The highest dose used in the rat study (60 mg/kg/day) resulted in a drug exposure (plasma AUC) that was about 15% of the maximum human value (at clinical dose of 30mg/kg). In the mouse study, the highest doses of 200 mg/kg/day (males) and 300 mg/kg/day (females) resulted in drug exposures that were respectively slightly lower and slightly above the maximum human value.

Effect on fertility: Fertility was unaffected in rats with doses of up to 75 mg/kg/day which resulted in a drug exposure (plasma AUC) that was less than the maximum human value.

Use in Pregnancy (Category C)

Deferasirox was not teratogenic in rats or rabbits treated with doses up to and exceeding the maximum tolerated doses. Fetal developmental impairment and increased skeletal variations were seen in rats at a maternotoxic dose of 100 mg/kg/day which achieved a drug exposure (plasma AUC) that was similar to the maximum human value. No adverse effects on fetal development was observed in rabbits at a maternotoxic dose of 50 mg/kg/day which achieved a drug exposure about 30% of the maximum human value. Treatment of rats with a maternotoxic dose of 90 mg/kg/day from early gestation to end of lactation resulted in increased stillborn pups and reduced pup birthweight. No effect was seen with 30 mg/kg/day which achieved a drug exposure about 20% of the maximum human value.

Adequate and well-controlled studies in pregnant women have not been conducted. Deferasirox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

It is not known if deferasirox is secreted into human milk. In an animal study, deferasirox was present in the milk of rats at higher concentration than in maternal plasma. Because many drugs are excreted in human milk, women should be advised against breast-feeding while taking deferasirox.

INTERACTIONS WITH OTHER MEDICINES

Effect on Deferasirox on Drug Metabolizing Enzymes

Deferasirox inhibits human CYP3A4, CYP2C8, CYP1A2, CYP2A6, CYP2D6 and CYP2C19 *in vitro*. The clinical significance of deferasirox inhibition of CYP2A6, CYP2D6 and CYP2C19 is unknown.

Interaction with midazolam and other agents metabolised 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%. 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).

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%). 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 repaglinide and other agents metabolised 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%-164%) and 62% (90% CI: 42%-84%), respectively. 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. Therefore, the concomitant use of Exjade with theophylline is not recommended. When EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. For substances that are predominantly metabolised by CYP1A2 and that have narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.An interaction between EXJADE and other CYP1A2 substrates cannot be excluded. Use caution when EXJADE is administered with other drugs metabolized by CYP1A2 such as clozapine, cyclobenazprine, imipramine, haloperidol, fluvoxamine, mexiletine, naproxen, olanzapine, riluzole, tacrine, tizanidine, zileuton and zolmitriptan.

Other information

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

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.

The concomitant use of Exjade with cholestyramine may result in a decrease in Exjade efficacy. In a study in healthy volunteers, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox AUC.

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, 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 PRECAUTIONS).

ADVERSE EFFECTS

In clinical trials in patients with transfusional iron overload, 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. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see PRECAUTIONS).

In clinical trials in patients with transfusional iron overload, elevations of liver transaminases were reported in about 2% of patients. These were not clearly dose-related and many 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.

In a 1-year, randomized, double-blind, placebo-controlled study in patients with non transfusion-dependent thalassemia syndromes and iron overload, diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events reported by patients receiving 10 mg/kg/day of EXJADE. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8%, respectively, of patients receiving 10 mg/kg/day of EXJADE. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal were reported in 1.8% of patients treated with 10 mg/kg/day of EXJADE.

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 PRECAUTIONS).

Adverse Events in Clinical Trials:

The data in Table 3 displays the adverse events, regardless of causality, occurring in >5% of patients in either treatment group in the primary efficacy study 0107 in which 296 β-thalassaemia patients were treated with EXJADE and 290 patients received desferrioxamine as an active comparator.

Table 3 Adverse Events Occurring in >5% of β-thalassaemia Patients in the Comparative Trial

Preferred Term	EXJADE N=296 n (%)	Desferrioxamine N=290 n (%)
Pyrexia	56 (18.9)	69 (23.8)
Headache	47 (15.9)	59 (20.3)
Abdominal pain	41 (13.9)	28 (9.7)
Cough	41 (13.9)	55 (19.0)
Nasopharyngitis	39 (13.2)	42 (14.5)
Diarrhoea	35 (11.8)	21 (7.2)
Creatinine increased*	33 (11.1)	0 (0)
Influenza	32 (10.8)	29 (10.0)
Nausea	31 (10.5)	14 (4.8)
Pharyngolaryngeal pain	31 (10.5)	43 (14.8)
Vomiting	30 (10.1)	28 (9.7)
Respiratory tract infection	28 (9.5)	23 (7.9)
Bronchitis	27 (9.1)	32 (11.0)
Rash	25 (8.4)	9 (3.1)
Abdominal pain upper	23 (7.8)	15 (5.2)
Pharyngitis	23 (7.8)	30 (10.3)
Arthralgia	22 (7.4)	14 (4.8)

Preferred Term	EXJADE N=296 n (%)	Desferrioxamine N=290 n (%)
Acute tonsillitis	19 (6.4)	15 (5.2)
Fatigue	18 (6.1)	14 (4.8)
Rhinitis	18 (6.1)	22 (7.6)
Back pain	17 (5.7)	32 (11.0)
Ear infection	16 (5.4)	7 (2.4)
Urticaria	11 (3.7)	17 (5.9)

*includes 'blood creatinine increased' and 'blood creatinine abnormal'

The type and frequency of adverse events observed in patients with sickle cell disease and other rare anaemias were similar to those observed in patients with β-thalassaemia. The adverse event profile in patients <16 years of age was similar to that seen in adults, regardless of disease state.

In 49 adult β-thalassaemia patients treated for greater than 1 year and up to 3 years, the type and frequency of adverse events was similar to that seen in patients treated for up to 1 year.

Adverse reactions with suspected relationship to product:

The following adverse drug reactions, listed in Table 4, have been reported in clinical studies following treatment with EXJADE. Adverse reactions are ranked below using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 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
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, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	oesophagitis

Hepatobiliary disorders		
	Common:	transaminases increased
	Uncommon:	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders		
	Common:	rash, pruritus
	Uncommon:	pigmentation disorder
	Rare:	Erythema multiforme
Renal and urinary disorders		
	Very common:	blood creatinine increased
	Common:	proteinuria
	Uncommon:	renal tubulopathy (Fanconi's syndrome)
General disorders and administration site conditions		
	Uncommon:	pyrexia, oedema, fatigue

Spontaneously reported adverse reactions, presented in Table 5, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 5 Adverse drug reactions derived from spontaneous reports

Renal and urinary disorders
acute renal failure (mostly serum creatinine increases ≥ 2x upper limit of normal, and usually reversible after treatment interruption), tubulointerstitial nephritis
Hepatobiliary disorders
hepatic failure
Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, leukocytoclastic vasculitis, urticaria, alopecia
Immune system disorders
hypersensitivity reactions (including anaphylaxis and angioedema)

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

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

DOSAGE AND ADMINISTRATION

Transfusional iron overload

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

> 1000 microgram/L). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size. EXJADE is available in three tablet strengths (125 mg, 250 mg and 500 mg). Dosing recommendations are the same for adult, paediatric and elderly patients.

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.

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.

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

Dose adjustment: It is recommended that serum ferritin be monitored every month and that the dose of EXJADE is 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. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

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. If serum ferritin falls consistently below 500 µg/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 (see PRECAUTIONS).

In children aged between 2 and 5 years, exposure to deferasirox is lower than in adults. This age group may therefore require higher maintenance doses than adults. However, the initial dose should be the same as in adults, followed by individual titration.

Non-transfusion-dependent thalassemia syndromes

Dosage: 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 microgram/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation.

Starting dose: The recommended initial daily dose of EXJADE is 10 mg/kg body weight.

Dose adjustment: It is recommended that serum ferritin be monitored every month. Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 microgram/L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 20 mg/kg

are not recommended because there is no experience with doses above this level in patients with non transfusion-dependent thalassemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 microgram/L, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction is recommended to 10 mg/kg or less when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 microgram/L.

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

Instructions for Use

EXJADE should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day (see PHARMACOLOGY – Pharmacokinetics). The tablets should be dispersed by stirring in water, orange or apple juice until a fine suspension is obtained. If dispersing in juice, it is recommended that the tablets should be dispersed in about 20mL of water before dilution with the juice. After the suspension has been swallowed, any residue should be resuspended in a small volume of water or juice and swallowed. Do not disperse in milk or carbonated drinks. 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.

Patient Monitoring

Dosage adjustments in the presence of an adverse reaction:

Dosage adjustments are recommended for patients experiencing non-progressive elevations in serum creatinine, elevations in liver transaminases or those patients experiencing rash (see PRECAUTIONS).

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. Single doses of 80 mg/kg in iron overloaded thalassaemic patients have been tolerated, with only mild nausea and diarrhoea noted. Single doses up to 40 mg/kg in normal subjects have been well tolerated.

Acute signs of overdose may include nausea, vomiting, headache, and diarrhoea. Overdose should be managed with appropriate supportive measures.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

125 mg: Off-white, round, flat tablet with bevelled edge and imprinted with "J125" on one side and "NVR" on the other. Packs of 28 dispersible tablets.

250 mg: Off-white, round, flat tablet with bevelled edge and imprinted with "J250" on one side and "NVR" on the other. Packs of 28 dispersible tablets.

500 mg: Off-white, round, flat tablet with bevelled edge and imprinted with "J500' on one side and "NVR" on the other. Packs of 28 dispersible tablets.

Packs of 84 dispersible tablets are registered but not supplied in Australia.

Storage:
Store below 30 degrees Celsius, protect from moisture

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

Ò = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Poison schedule: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

July 2006.

DATE OF MOST RECENT AMENDMENT

24 October 2013

(exj241013i.doc) based on the CDS 15 July 2013