1. PRODUCT NAME

EXJADE™ (deferasirox) 125 mg, 250 mg, 500 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXJADE 125 mg dispersible tablets

Each dispersible tablet contains 125 mg deferasirox.

Excipient with known effect: Each dispersible tablet contains 136 mg lactose.

EXJADE 250 mg dispersible tablets

Each dispersible tablet contains 250 mg deferasirox.

Excipient with known effect: Each dispersible tablet contains 272 mg lactose.

EXJADE 500 mg dispersible tablets

Each dispersible tablet contains 500 mg deferasirox.

Excipient with known effect: Each dispersible tablet contains 544 mg lactose.

For full list of excipients, see section List of Excipients.

3. PHARMACEUTICAL FORM

Dispersible tablet.

125 mg: White to slightly yellow, 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: White to slightly yellow, 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: White to slightly yellow, round, flat tablet with bevelled edge and imprinted with "J500' on one side and "NVR" on the other. Packs of 28 dispersible tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Dose and method of administration

Dose

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 individualised 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.

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).

Maintenance dose:
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 and to minimise the risk of overchelation (See Special Warnings and Precautions for Use). 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 (See Special Warnings and Precautions for Use).

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. 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 Special Warnings and Precautions for Use).

Patients with hepatic impairment:
Deferasirox 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 Special Warnings and Precautions for Use and Pharmacological Properties). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (See Special Warnings and Precautions for Use).

Paediatric patients:
The dosing recommendations for paediatric patients are the same as for adult patients. It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see Special Warnings and Precautions for Use). 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. 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.

Method of administration
EXJADE dispersible tablets must be taken once daily on an empty stomach at least 30 minutes before food, 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. After the suspension has been swallowed, any residue must be re-suspended 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.

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

High risk myelodysplastic syndrome (MDS) patients and patients with other haematological and non-haematological 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.

4.4 Special warnings and precautions for use
The decision to remove accumulated iron should be individualised based on anticipated clinical benefit and risks of chelation therapy (see Dose and Method of Administration).

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

Renal Impairment

EXJADE has not been studied in patients with renal impairment and must be used with caution in such patients. EXJADE treatment has been initiated only in patients with serum creatinine within the age-appropriate normal range. Deferasirox is minimally excreted (8% of the dose) via the kidney (see Pharmacological Properties).

Non-progressive rises in serum creatinine have been noted in patients treated with deferasirox, usually within the normal range. This has been observed in both paediatric and adult patients with iron overload during the first year of treatment. A study which assessed the renal function of patients enrolled in the registration studies up to 13 years later, confirmed the non-progressive nature of these serum creatinine observations.

Cases of acute renal failure have been reported following the post-marketing use of deferasirox (see Undesirable Effects). Although causal relationship with EXJADE could not be established there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

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. Therefore serum creatinine and/or creatinine clearance should be monitored weekly 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 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.

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

Dose reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated.

Tests for proteinuria should be performed monthly.

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

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 Dose and Method of 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.

The recommendations for renal function monitoring are summarized in Table 1.

Table 1 Recommendations for renal function monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and/or	Twice (2x)
Contraindicated	>2 times age-appropriate ULN*	or	<40 mL/min
Monitoring	**Monthly**	**and/or**	**Monthly**
	For patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress the renal function as they may be more at risk of complications in the first month after initiation, or modification of therapy (including switching formulation), monitoring should be:		
	Weekly	**and/or**	**Weekly**
Reduction of daily dose by 10 mg/kg/day if the following renal parameters are observed on two consecutive visits and cannot be attributed to other causes:			
Adult patients	>33% above pre-treatment average (non-progressive rise)		
Paediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and paediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic Impairment

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh C). (See Dose and Method of Administration and Pharmacological Properties). Deferasirox 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 was not influenced by such transaminase levels. Deferasirox is principally eliminated by glucuronidation and is minimally (about 8%) metabolised by oxidative cytochrome P450 enzymes (see Pharmacological Properties).

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 post-marketing reports of hepatic failure in patients treated with deferasirox. 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 Undesirable 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.

Blood Disorders

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see Undesirable Effects). The relationship of these episodes to treatment with deferasirox 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.

Gastrointestinal Disorders

Gastrointestinal irritation may occur during EXJADE treatment. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. 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 Undesirable 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. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

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 Interaction With Other Medicines and Other Forms of Interaction), and in patients with platelet counts $<50 \times 10^9$/L.

Hypersensitivity Reactions

Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see Undesirable Effects). If reactions are severe, EXJADE should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced previous hypersensitivity reactions on Exjade due to the risk of anaphylactic shock.

Skin Disorders

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. Patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If any SCAR is suspected EXJADE should be discontinued immediately and should not be reintroduced.

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.

Vision and Hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment (see Undesirable Effects). 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.

Other Considerations

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. It is recommended that serum ferritin be measured every month in order to assess the patient's response to therapy and to avoid overchelation. Closer monitoring of serum ferritin levels, as well as renal and hepatic function is recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. Dose reduction may be considered to avoid overchelation (see Dose and Method of 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 and minimise the risk of overchelation. If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered.

Deferasirox has not been associated with growth retardation in children followed for up to 5 years in clinical trials with the dispersible tablet formulation. However, as a general precautionary measure, body weight and longitudinal growth in paediatric patients can be monitored at regular intervals (every 12 months).

Lactose content

The dispersible tablets contain lactose (1.1 mg lactose for each me 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.

4.5 Interaction with other medicines and other forms of interaction

Agents That May Decrease EXJADE Systemic Exposure

In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg dispersible tablet formulation) 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 Food

The bioavailability of deferasirox dispersible tablets was increased to a variable extent when taken along with food. EXJADE must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see Dose and Method of Administration).

Interaction with Midazolam and Other Agents Metabolised by CYP3A4

In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablet 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. cyclosporin, simvastatin, hormonal contraceptive agents).

Interaction with Repaglinide and Other Agents Metabolised by CYP2C8

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

Interaction with Theophylline and Other Agents Metabolised by CYP1A2

In a healthy volunteer study, the concomitant administration of deferasirox (repeated dose of 30 mg/kg/day dispersible tablet formulation) 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. When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates may be possible.

Interaction with busulfan

Based on literature reports, concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC). The AUC increase ranged approximately 40 to 150%. The mechanism of the interaction remains unclear. Caution should be exercised when deferasirox is combined with busulfan and the patient's plasma concentrations of busulfan should be monitored.

Other Information

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

The concomitant administration of deferasirox 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 safety profile of deferasirox in combination with other iron chelators (deferoxamine, deferiprone) observed in clinical trials, post-marketing experience or published literature (as applicable) was consistent with that characterized for monotherapy.

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

Concomitant administration of deferasirox with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see Special Warnings and Precautions for Use).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Animal studies showed that deferasirox was not teratogenic in rats or rabbits, 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. Deferasirox did not cause other effects on fertility or reproduction (see Preclinical Safety Data). The potential risk for humans is unknown.

Caution should be exercised when deferasirox is combined with hormonal contraceptive agents that are metabolised through CYP3A4 due to a possible decrease in efficacy of contraceptive agents (see Interaction With Other Medicines and Other Forms of Interaction)

Pregnancy

No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see Preclinical 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

It is not known if deferasirox is secreted into human milk. In animal studies, deferasirox was found to be rapidly and extensively transferred into maternal milk. No effects on the offspring were noted at maternally non-toxic doses of deferasirox. Breast-feeding while taking EXJADE is not recommended.

Fertility

Deferasirox did not affect fertility or reproduction in rat studies even at toxic doses (see Preclinical Safety Data).

4.7 Effects on ability to drive and use 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.

4.8 Undesirable effects

Summary of the Safety Profile

The most frequent reactions reported during chronic treatment with the deferasirox dispersible tablet formulation 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 Special Warnings and Precautions For Use).

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 the deferasirox dispersible tablet formulation. 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 deferasirox. 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.

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

The following adverse drug reactions, listed in Table 2, have been reported in clinical studies following treatment with deferasirox dispersible tablet. 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 2 Adverse drug reactions reported in clinical studies

Psychiatric disorders		
	Uncommon:	anxiety, sleep disorder
Nervous system disorders		
	Common:	headache
	Uncommon:	dizziness
Eye disorders		
	Uncommon:	cataract, maculopathy
	Rare:	optic neuritis
Ear and labyrinth disorders		
	Uncommon:	deafness
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	laryngeal pain
Gastrointestinal disorders		
	Common:	diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia

Uncommon:	gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis
Rare:	oesophagitis
Hepatobiliary disorders	
Common:	transaminases increased
Uncommon:	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritus
Uncommon:	pigmentation disorder
Rare:	erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	
Very common:	blood creatinine increased
Common:	proteinuria
Uncommon	renal tubular disorder (Fanconi syndrome)
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 3, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 3 Adverse drug reactions derived from spontaneous reports (frequency not known)

Renal and urinary disorders
renal tubular necrosis, acute renal failure (mostly serum creatinine increases ≥ 2x upper limit of normal, and usually reversible after treatment interruption), tubulointerstitial nephritis
Gastrointestinal disorders
Gastrointestinal perforation
Hepatobiliary disorders
hepatic failure

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
Blood and lymphatic system disorders
Pancytopenia
Immune system disorders
hypersensitivity reaction (including anaphylactic reaction and angioedema)
Metabolism and nutrition disorders
Metabolic acidosis

Description of selected adverse drug reactions

Cytopenias

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia, thrombocytopenia, and aggravated anaemia in patients treated with deferasirox. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see Special Warnings and Precautions For Use). The relationship of these episodes to treatment with deferasirox is uncertain.

Pancreatitis

Cases of serious acute pancreatitis were observed with and without documented underlying biliary conditions.

Paediatric population

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

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrolment) with transfusional hemosiderosis received deferasirox, there were no unexpected safety findings regarding adverse events (AEs) or laboratory abnormalities. Increases in serum creatinine of >33% and above the upper limit of normal (ULN) on ≥2 consecutive occasions were observed in 3.1% of children and elevation of alanine aminotransferase (ALT) greater than 5 times the ULN was reported in 4.3% of children. The most frequently observed AEs with reported suspected relationship to study drug were increase in ALT (21.1%), increase in aspartate aminotransferase (AST, 11.9%), vomiting (5.4%), rash (5.0%), increase in blood creatinine (3.8%), abdominal pain (3.1%) and diarrhoea (1.9%). Overall growth and development were not affected in this paediatric population.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Single doses up to 40 mg/kg in normal subjects have been well tolerated.

Early signs of acute overdose are digestive effects such as abdominal pain, diarrhoea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.

There is no specific antidote for deferasirox. Standard procedures for management of overdose (e.g. induction of emesis or gastric lavage) may be indicated as well as symptomatic treatment, as medically appropriate.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Pharmacodynamic effects

In an iron balance metabolic study in iron overloaded adult thalassaemic patients, deferasirox at daily doses of 10, 20 and 40 mg/kg (dispersible tablet formulation) induced the mean net excretion of 0.119, 0.329, and 0.445 mg Fe/kg body weight/day, respectively.

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

Daily treatment with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassemia 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. 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. Deferasirox induced similar responses in iron overloaded patients with other anaemias. Daily doses of 10 mg/kg (dispersible tablet formulation) 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 Dose and Method of Administration). 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.

In patients with cardiac iron deposition (MRI T2* <20 ms), treatment with deferasirox was shown to remove cardiac iron as demonstrated by progressive improvements in T2* values over 3 years of observation. In patients without cardiac deposition, deferasirox was shown to prevent clinically relevant cardiac iron deposition (maintenance of T2* at >20 ms) over 1 year of observation, despite significant ongoing transfusion exposure.

Clinical efficacy and safety

Clinical efficacy studies were conducted with deferasirox dispersible tablets. An open-label, randomised, Phase III, active comparator control study to compare deferasirox dispersible tablets and Desferal (deferoxamine) was conducted in patients with beta-thalassemia and transfusional haemosiderosis. Patients ≥2 years of age were randomised in a 1:1 ratio to receive either oral deferasirox at starting doses of 5, 10, 20 or 30 mg/kg once daily or subcutaneous deferoxamine 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 randomised to deferoxamine who had LIC values <7 mg Fe/g dw were permitted to continue on their prior deferoxamine 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. Deferasirox 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 randomised. Demographics were well balanced. Fifty-one percent of the patients were <16 years of age. The overall success rates were 52.9% for deferasirox 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 4). 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 (deferasirox doses of 20 or 30 mg/kg and deferoxamine doses of ≥35 mg/kg). The success rates with deferasirox 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 deferasirox 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 deferasirox doses of 5 to 30 mg/kg were also observed (Table 4).

Table 4 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 (µg/L) Mean change from baseline ± SD**	
Defer-asirox	Defer-oxamine	Defer-asirox	Defer-oxamine	Deferasirox Mean ± SD (n)	Defer-oxamine Mean ± SD (n)	Deferasirox Mean ± SD (n)	Defer-oxamine Mean ± SD (n)
5	20-30	6.2 ± 1.6	33.9 ± 9.9	0.58 ± 0.328 (15)	0.95 ± 0.101 (13)	+1189 ± 700 (15)	+211 ± 459 (13)
10	25-35	10.2 ± 1.2	36.7 ± 9.2	0.67 ± 0.365 (68)	0.98 ± 0.217 (75)	+833 ± 817 (73)	+32 ± 585 (77)
20	35-50	19.4 ± 1.7	42.4 ± 6.6	1.02 ± 0.398 (77)	1.13 ± 0.241 (87)	-36 ± 721 (80)	-364 ± 614 (89)
30	≥50	28.2 ± 3.5	51.6 ± 5.8	1.67 ± 0.716 (108)	1.44 ± 0.596 (98)	-926 ± 1416 (115)	-1003 ± 1428 (101)

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

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 deferasirox 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 haemosiderosis. This study was an open-label, randomised, Phase II study of the safety and efficacy of deferasirox dispersible tablets relative to deferoxamine given for 1 year. Patients were randomised to deferasirox 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 deferasirox 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 deferasirox (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

A placebo-controlled randomized trial was performed in 225 patients with MDS (Low/Int-1 risk) and transfusional iron overload of which 149 were treated with deferasirox and 76 received placebo. The observed hazard ratio of 0.64 (95% CI: 0.42, 0.96) suggests a positive impact of deferasirox on event-free survival (EFS, a composite endpoint defined as death, worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, or progression to acute myeloid leukemia, whichever occurred first).

The safety profile was consistent with previous studies in adult MDS patients.

A cardiac sub-study was conducted as part of a Phase IV study with deferasirox dispersible tablets. 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 ≥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 to 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 ± coefficient of variation) significantly increased from a baseline value of 11.2 ms ± 40.5% to 12.9 ms ± 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 ± 5.7% to 67.1 ± 6.0%. In the prevention cohort, myocardial T2* remained within the normal range and was unchanged from a baseline value of 32.0 ms ± 25.6% to 32.5 ms ± 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.

Patients in the treatment cohort of the 1-year core study had the option to participate in two 1-year extensions. Over a three-year treatment duration period, there was a statistically significant (p<0.0001), progressive and clinically relevant increase in the geometric mean of cardiac T2* from baseline overall, in the severe cardiac iron overload sub-group, which is associated with a high risk of cardiac failure (T2* >5 to <10 ms), and in the mild to moderate cardiac iron overload sub-group (T2* 10 to <20 ms) (Table 5). Using the geometric mean ratio, the T2* increase was 43% above baseline in all patients, 37% increase from baseline in the T2* >5 to <10 ms sub-group, and 46% increase from baseline in the T2* 10 to <20 ms sub-group. Continuous treatment with deferasirox dispersible tablets for up to 3 years at

doses >30 mg/kg/day effectively reduced cardiac iron in thalassemia major patients with myocardial siderosis as shown by the number of patients who normalised their T2* or improved to a category associated with a lower risk of cardiac failure (Table 6).

Table 5 Geometric mean of T2 (ms) at baseline, and at the end of year 1, 2, and 3*

Baseline cardiac T2* sub-group	**Baseline (year 0)**	**End of core (year 1)**	**End of E1 (year 2)**	**End of E2 (year 3)**
Overall	11.20 (n=105)	12.9 (n=105) (p<0.0001)	14.79 (n=95) (p<0.0001)	17.12 (n=68) (p<0.0001)
T2* >5 to <10 ms	7.39 (n=41)	8.15 (n=41)	8.71 (n=35)	10.53 (n=24)
T2* 10 to <20 ms	14.62 (n=64)	17.39 (n=64)	20.13 (n=60)	22.32 (n=44)

E1 = end of first year extension
E2 = end of second year extension

Table 6 Transition table of cardiac T2 from core baseline to end of E2 (year 3)*

Baseline cardiac T2* sub-group	**Baseline n (%)**	**<5 ms n (%)**	**5 - <10 ms n (%)**	**10 - <20 ms n (%)**	**≥20 ms n (%)**	**Missing n (%)**
>5 - <10 ms (N=39)	39 (100.0)	1 (2.6)	18 (46.2)	15 (38.5)	1 (2.6)	4 (10.3)
10 - <20 ms (N=62)	62 (100.0)		4 (6.5)	16 (25.8)	40 (64.5)	2 (3.2)
All patients (N=101)	101 (100.0)	1 (1.0)	22 (21.8)	31 (30.7)	41 (40.6)	6 (5.9)

5.2 Pharmacokinetic properties

Absorption:

Deferasirox (dispersible tablet formulation) is 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 (dispersible tablet formulation) was about 70% compared to an intravenous dose. Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approx. 13 to 25%) elevated when taken 30 minutes before meals with normal or high fat content. 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:
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 L in adults.

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. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No inhibition of deferasirox metabolism by hydroxyurea was observed in vitro. 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 elimination half-life ($T_{1/2}$) ranged from 8 to 16 hours.

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.

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. 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. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

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

Renal or hepatic impairment:
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 section Dose and Method of Administration and Special Warnings and Precautions for Use). The pharmacokinetics of deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

5.3 Preclinical 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 and lens opacity (cataracts). Similar findings were observed in neonatal and juvenile animals. The kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron.

The potential for toxicity to reproduction was assessed in rats and rabbits. 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. Deferasirox did not cause other effects on fertility or reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Crospovidone

Microcrystalline cellulose

Povidone (K30)

Sodium lauryl sulphate

Silicon dioxide

Magnesium stearate

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

Exjade must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Blister pack PA/Al/PVC.

Packs containing 28 or 84 dispersible tablets.

Blister pack PVC/PE/PVdC

Packs containing 28 or 84 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

New Zealand

Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

9th February 2012

10 DATE OF REVISION OF THE TEXT

27 March 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.9 - Overdose	Update text in line with data sheet explanatory guide v1.3

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