SCHEDULING STATUS: **S4**

NAME OF THE MEDICINE

EXJADE 125 mg dispersible tablets

EXJADE 250 mg dispersible tablets

EXJADE 500 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXJADE 125 mg dispersible tablets contains 125 mg deferasirox

EXJADE 250 mg film-coated tablets contains 250 mg deferasirox

EXJADE 500 mg dispersible tablets contains 500 mg deferasirox

EXJADE contains lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet

EXJADE 125 mg tablets

Off-white, round, flat, bevelled edge tablet, with “J125” imprinted on the one side and “NVR” on the other.

EXJADE 250 mg tablets

Off-white, round, flat, bevelled edge tablet, with “J250” imprinted on the one side and “NVR” on the other.

EXJADE 500 mg tablets

Off-white, round, flat, bevelled edge tablet, with “J500” imprinted on the one side and “NVR” on the other.

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).

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

EXJADE 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).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

EXJADE 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 (100-200 ml) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be resuspended in a small volume of water or juice and swallowed.

The tablets must not be chewed or swallowed whole (See Interaction with other medicinal products and other forms of interaction).

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

Posology

Transfusional iron overload

Dosage

It is recommended that therapy with EXJADE be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin > 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).

The decision to remove accumulated iron should be individualised based on anticipated clinical benefit and risks of chelation therapy.

Starting dose

The starting dose is determined by the frequency of blood transfusions.

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.)

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).

For patients already well-managed on treatment with deferoxamine, a starting dose of EXJADE that is numerical 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)..

Non-transfusion-dependent thalassaemia syndrome

Dosage

EXJADE 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 minimise 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 to assess the patients's response to therapy and to minimize the risk of overchelation (see "Special warnings and precautions for use". 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 thalassaemia 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.

Special Populations

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 elderly patients should be monitored closely for adverse reactions that may require a dose adjustment.

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. (see Contraindications)

EXJADE should not be used by patients with CrCl below 60 mL/min. (see Contraindications)

The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 10 mg/kg (see section Special Warnings and Precautions for use).

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.

Patients with hepatic impairment

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 Contraindications). Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. (See section Special Warnings and Precautions for use).

Paediatric Population

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.

4.3 CONTRAINDICATIONS

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

- Creatinine clearance < 60 mL/min
- Repaglinide (see Interaction with other medicinal products and other forms of interaction)
- High risk myelodysplastic syndrome (MDS) patients and patients with other haematological and nonhaematological malignancies with limited expected survival (< 1 year) who are not expected to benefit from chelation therapy due to the rapid progression of their disease.
- Severe hepatic impairment (Child-Pugh C)
- Pregnancy and lactation (See Fertility, pregnancy and lactation)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant administration of EXJADE with medicine 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 complications such as ulceration and haemorrhage.

There have been post marketing 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.

The decision to remove accumulated iron should be individualised based on anticipated clinical benefit and risks of chelation therapy.

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

Renal impairment

Non-progressive rises in serum creatinine have been noted in patients treated with EXJADE, usually within the normal range. Cases of acute renal failure have been reported (See Undesirable effects). Although causal relationship with EXJADE could not be established, there have been 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 other 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 (including switching formulation) and monthly thereafter. EXJADE should not be used in patients with creatinine clearance less than 60 mL/min (see Contraindications).

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.

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 section 4.2 Posology and method of administration)

The recommendations for renal function monitoring are summarized in the 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 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)		
Pediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and pediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see Contraindications). Deferasirox is principally eliminated by glucuronidation and is minimally (about 8 %) metabolised by oxidative cytochrome P450 enzymes.

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 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.

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 haemorrhage, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients. Medical practitioners 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 medicines that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts <50 x 109/L.

Skin disorders

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinaphilia and systemic symptoms (DRESS) which could be life-threatening or fatal**.** 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.

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

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

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with EXJADE treatment (see Section 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.

Blood disorders

There have been post marketing reports (both spontaneous and from clinical trials) of anaemia or detection of aneamia and other cytopenias in patients treated with EXJADE. Although most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see section Undesirable effects) the contribution of EXJADE could not always be excluded.

Blood counts should be monitored regularly. Dose interruption of treatment with EXJADE should be considered in patients who develop unexplained anaemia or other cytopenias. Reintroduction of therapy with EXJADE may be considered, once the cause of the cytopenia has been elucidated.

Body weight and longitudinal growth in paediatric patients should be monitored at regular intervals (every 12 months).

Monthly monitoring of serum ferritin is recommended 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 "Posology and method of administration").

Lactose

The tablets contains lactose (1,1 mg lactose for each mg of deferasirox). This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicine 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 complications such as ulceration and haemorrhage.

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% (9 0% CI: 8 % - 26 %). In the clinical setting, this effect may be more pronounced.

Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

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 Cmax by 131 % (90 % CI: 103 % - 164 %) and 62 % (90 % CI: 42 % - 84 %), respectively. 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.

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.

When EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between EXJADE and other CYP1A2 substrates may be possible.

Interaction with food

The bioavailability of EXJADE 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 section Dosage and directions for use).

Information on dispersion of EXJADE in fruit juices other than orange and apple is not available.

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/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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Safety in pregnancy and lactation has not been established. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown.

EXJADE should not be used during pregnancy (See Contraindications).

Breast-feeding

In animal studies, EXJADE was found to be rapidly and extensively secreted into maternal milk. It is not known if EXJADE is secreted into human milk. Breast-feeding while taking EXJADE is not recommended

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 dizziness should exercise caution when driving or operating machinery (see Undesirable effects).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

In clinical trials in patients with transfusional iron overload, the most frequent reactions reported during chronic treatment with EXJADE in adult and paediatric patients included 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. 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 section Special Warnings and Precautions for use).

In clinical trials in patients with transfusional iron overload, elevations of liver transaminases were reported in about 2 % of patients. These were not dependent on dose and most of these patients had elevated levels prior to receiving EXJADE. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0,3 %).

There have been post marketing 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 thalassaemia 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

High-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with EXJADE (see section Special Warnings and Precautions for use).

The following adverse reactions, listed in Table 2, 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 (≥ 1/1000, < 1/100); rare (>1/10 000, < 1/1000); 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:	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:	Gastritis, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, acute pancreatitis
	Rare	oesophagitis
Hepatobiliary disorders		

	Common:	Increased transaminases
	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:	Increased blood creatinine
	Common:	proteinuria
	Uncommon	renal tubulopathy (Fanconi's syndrome)
General disorders and administration site conditions		
	Uncommon:	pyrexia, oedema, fatigue

Post marketing side effects

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

Renal and urinary disorders:

Renal tubular necrosis, acute renal failure (serum creatinine increases > 2 x upper limit of normal), (See "Special warning and precautions for use") tubulointerstitial nephritis

Blood and lymphatic system disorder:

Anaemia

Gastrointestinal disorders:

Gastrointestinal perforatio

Pancreatitis

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

Hepatobiliary disorders:

Hepatic failure

Skin and subcutaneous disorders

Stevens-Johnson syndrome, Leukocytoclastic vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN).

Immune system disorders

Hypersensitivity reactions (including anaphylaxis and angioedema)

There have been post marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia and thrombocytopenia and aggravated anaemia in patients treated with EXJADE. 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 EXJADE is uncertain (See "Special warnings and precautions for use").

Paediatric population

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

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) 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 diarrhea (1.9 %). Overall growth and development were not affected in this pediatric population**.**

4.9 OVERDOSE

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

Early sign 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 with 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**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification:

A 27 Chelating agents (versenates) as heavy metal antidotes.

Deferasirox is an orally active chelator that is 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.

5.2 PHARMACOKINETICS PROPERTIES

Absorption

Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1,5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from deferasirox tablets is 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. 13-25 %) 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 (t1/2) 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 have not been studied in elderly patients (aged 65 or older).

Renal or hepatic impairment

In a single dose study, 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.Deferasirox should not be used in patient with severe hepatic impairment (Child-Pugh C). The pharmacokinetics of deferasirox have not been studied in patients with renal impairment

6 PHARMACUETICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, crospovidone, microcrystalline cellulose, povidone (K30), sodium lauryl sulphate, silicon dioxide, magnesium stearate

Contains lactose monohydrate

6.2 INCOMPATIBILITIES.

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C in the original package. Protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF THE CONTAINER

28 or 84 dispersible tablets in blisters composed of a colourless, transparent PVC/PE/PVDC polyvinylchloride/ polyethylene/ polyvinylidene chloride) film with an aluminium foil backing, or a PA/Al/PVC (polyamide /aluminium /polyvinylchloride) film with an aluminium foil backing. Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis SA (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

8. REGISTRATION NUMBERS:

Exjade 125 mg: A40/27/0266

Exjade 250 mg: A40/27/0267

Exjade 500 mg: A40/27/0268

9. DATE OF FIRST AUTHORISATION

2 March 2007

10. DATE OF REVISION OF THE TEXT

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2019-PSB/GLC-1065-s, 2018-PSB/GLC-0934-s, 2017-PSB/GLC-0882-s, 2015-PSB/GLC-0763-s,

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Exjade 125 mg:	
Namibia: 08/27/0122	NS2
Botswana: BOT0901591A	S2
Exjade 250 mg:	
Namibia: 08/27/0123	NS2
Botswana: BOT0901593A	S2
Exjade 500 mg:	
Namibia: 08/27/0124	NS2
Botswana: BOT0901592A	S2