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NOVARTIS

10th July 2008

IMPORTANT SAFETY INFORMATION

Re: Direct Healthcare Professional Communication regarding EXJADE® (deferasirox) And hepatic failure / need for hepatic monitoring, gastrointestinal haemorrhage and ulceration, and renal tubulopathy

Dear Healthcare Professional,

In agreement with EU regulatory authorities, including the Irish Medicines Board (IMB),Novartis wishes to provide you with the following updated safety information regarding Exjade® (deferasirox) which is indicated for the treatment of chronic iron overload due to frequent blood transfusions or when deferoxamin is contraindicated or inadequate.

- **Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with Exjade. The role of Exjade as a contributing or aggravating factor cannot be excluded. It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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 treatment should be interrupted (see section 4.8).**

- **Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving Exjade. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during Exjade therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected.**

- **Cases of renal tubulopathy (Fanconi's syndrome) have been reported in patient treated with EXJADE®. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.**

Changes to the product information (Summary of Product Characteristics [SPC] and Package leaflet [PL]) have been recommended (section 4.4, 4.5 and 4.8) and a European Commission decision implementing these changes is awaited.

Healthcare professionals are encouraged to report any suspected adverse reactions associated with the use of Exjade.

Further information on the safety concerns

The new information follows a review of the available data as part of the periodic safety reviews of the product. Details of the findings supporting the addition of the three safety topics are described below:

Hepatic failure:

There have been reports of hepatic failure in patients treated with Exjade, some with a fatal outcome. Most of these reports involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure. However, the role of Exjade as a contributing or aggravating factor cannot be excluded. No patient with normal baseline liver function or without additional life-threatening complications of their underlying disease has developed hepatic failure.

Updated monitoring recommendations are included in the product information.

Gastrointestinal hemorrhage and ulceration, and oesophagitis:

There have been reports of GI hemorrhage and upper GI ulceration, sometimes in combination. Some cases were reported in paediatric patients. Some of the patients were taking concomitant medications that are known to predispose to these events (NSAIDs, corticosteroids, anti-coagulants or oral bisphosphonates) and some had severe pre-existing thrombocytopenia. In addition, a total of seven reasonably well documented cases of oesophagitis have been reported. The following adverse drug reactions have therefore been added to the Exjade SPC: gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer and oesophagitis.

Renal tubulopathy (acquired Fanconi's syndrome):

Acquired Fanconi's syndrome is a condition which is characterised by wasting of glucose, phosphate, uric acid and various ions from the proximal renal tubules. Some patients also have renal tubular acidosis (RTA). Cases of renal tubular disorders and RTA (collectively termed acquired Fanconi's syndrome) have been reported in patients treated with Exjade.

- Since the initial approval in 2006, the SPC for Exjade recommends monthly tests for proteinuria (additional markers of renal tubular function, e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate,

phosphaturia, aminoaciduria, may also be monitored); and that dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

Further information on recommendations to healthcare professionals
Not applicable.

Call for reporting

In the meantime, healthcare professionals should continue to report all serious adverse events suspected to be associated with the use of Exjade to Novartis Ireland Limited (see address below) and/or the IMB at the following address:

Pharmacovigilance Section,
Irish Medicines Board,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2.

Communication information
If you have any further questions, please do not hesitate to contact Novartis Ireland at the below address.
Please find enclosed the text of the revised SPC for each strength (with changes made visible). As mentioned above this is a pre-European Commission decision version of the SPC.

Kind regards,

Dr Hakan Granlund
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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 125 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 125 mg deferasirox.

This product contains lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 125 on the other).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).

4.2 Posology and method of administration

Treatment with EXJADE should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions. It is recommended that treatment 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 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

Deleted: EXJADE is available in three tablet strengths (125 mg, 250 mg and 500 mg).

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 who require reduction of elevated body iron levels and who are also 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 who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

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). When this results in a daily dose less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

Maintenance dose
It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Doses above 30 mg/kg are not recommended because there is only limited experience with doses above this level. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Preparation
EXJADE must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day (see sections 4.5 and 5.2). The tablets are dispersed by stirring in a glass of water or orange or apple juice (100 to 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 also section 6.2).

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above.

Paediatric patients (2 to 17 years of age)
The dosing recommendations for paediatric patients are the same as for adult patients. Changes in weight of paediatric patients over time must be taken into account when calculating the dose. In children aged between 2 and 5 years, exposure is lower than in adults (see section 5.2). This age group may therefore require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, followed by individual titration.

Patients with renal impairment
EXJADE has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min (see sections 4.3 and 4.4).

Patients with hepatic impairment
EXJADE has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as described above. Hepatic function in all patients should be monitored before treatment then every month (see section 4.4).

4.3 Contraindications

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

Combination with other iron chelator therapies as the safety of such combinations has not been established (see section 4.5).

Patients with estimated creatinine clearance <60 ml/min.

4.4 Special warnings and precautions for use

Renal function:

EXJADE has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Cases of acute renal failure have been reported following post-marketing use of EXJADE (see section 4.8).

The causes of the rises in serum creatinine have not been elucidated. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are receiving high doses of EXJADE and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult).

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, creatinine clearance** (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels **should be monitored weekly in the first month after initiation or modification of therapy with EXJADE, and monthly thereafter**. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting.

For adult patients, the daily dose may be reduced by 10 mg/kg if a rise in serum creatinine by >33% above the average of the pre-treatment measurements and estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) are seen at two consecutive visits, and cannot be attributed to other causes (see section 4.2). For paediatric patients, the dose may be reduced by 10 mg/kg if estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) and/or serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

After a dose reduction, for adult and paediatric patients, treatment should be interrupted if a rise in serum creatinine >33% above the average of the pre-treatment measurements is observed and/or the calculated creatinine clearance falls below the lower limit of the normal range. Treatment may be reinitiated depending on the individual clinical circumstances.

Particular attention should also be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function.

Tests for proteinuria should be performed monthly. As needed, additional markers of renal tubular function (e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria) may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

If, despite dose reduction and interruption, the serum creatinine remains significantly elevated and there is also persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome), the patient should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered.

Hepatic function:

Liver function test elevations have been observed in patients treated with EXJADE. Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with EXJADE. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However,

Deleted: EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).¶
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the role of EXJADE as a contributing or aggravating factor cannot be excluded (see Section 4.8).

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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 can not be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

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EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving EXJADE. Multiple ulcers have been observed in some patients (see section 4.8). Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal 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 Section 4.5 Interaction with other medicinal products and other forms of interaction).

Skin rashes may appear during EXJADE treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration.

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 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported (see section 4.8). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy (see section 4.2). If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends. The results should also be noted in the provided patient's booklet.

In the 1-year clinical studies growth and sexual development of paediatric patients treated with EXJADE were not affected. However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored at regular intervals (every 12 months).

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE.

The tablets contain lactose (1.1 mg lactose for each mg of deferasirox). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

The concomitant use of deferasirox with aluminium-containing antacid preparations is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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, it is not recommended to take EXJADE tablets with aluminium-containing antacid preparations (see section 4.4).

The bioavailability of deferasirox 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 sections 4.2 and 5.2).

Deferasirox metabolism depends on UGT enzymes. A decrease of its plasma concentration cannot be excluded when it is given with potent UGT inducers such as rifampicin, phenobarbital or phenytoin. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

In a healthy volunteer study, the concomitant administration of EXJADE and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17% (90% 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, bepridil, ergotamine).

The safety of EXJADE in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies (see section 4.3).

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

An interaction between deferasirox and CYP2C8 substrates like paclitaxel and repaglinide cannot be excluded.

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 administration of EXJADE and substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids, or oral bisphosphonates, as well as anticoagulants may increase the risk of gastrointestinal toxicity (see section 4.4). EXJADE may also increase the hemorrhage risk of anticoagulants. A close clinical monitoring should be exercised when deferasirox is combined with these drugs.

4.6 Pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see section 5.3). The potential risk for humans is unknown.

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

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

Fertility
No fertility data is available for humans. In animals, no adverse effects on male or female fertility were

found (see section 5.3).

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 reaction of dizziness should exercise caution when driving or operating machinery (see section 4.8).

4.8 Undesirable effects

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. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Indeed, in some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction (see section 4.4).

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse drug reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During postmarketing experience, hepatic failure, sometimes fatal, has been reported with Exjade, especially in patients with pre-existing liver cirrhosis (see section 4.4). As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with EXJADE (see section 4.4).

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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); not known (cannot be estimated form the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Nervous system disorders		
	Common:	Headache
	Uncommon:	Dizziness
Eye disorders		
	Uncommon:	Early cataract, maculopathy
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
Renal and urinary disorders		
	Very common:	Blood creatinine increased
	Common:	Proteinuria

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	Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
	Not known	Acute renal failure[1]
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus
	Uncommon:	Pigmentation disorder
	Not known:	Urticaria[1]
General disorders and administration site conditions		
	Uncommon:	Pyrexia, oedema, fatigue
Immune system disorders		
	Not known	Hypersensitivity reactions (including anaphylaxis and angioedema)[1]
Hepatobiliary disorders		
	Common:	Transaminases increased
	Uncommon:	Hepatitis, cholelithiasis
	Not known:	Hepatic failure[1]
Psychiatric disorders		
	Uncommon:	Anxiety, sleep disorder

[1] Adverse reactions reported during postmarketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

4.9 Overdose

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

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.

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 411 adult (age ≥16 years) and 292 paediatric patients (aged 2 to <16 years) with chronic iron overload due to blood transfusions. Of the paediatric patients 52 were aged 2 to 5 years. 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).

Daily treatment at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/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. EXJADE induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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. Limited clinical data (29 patients with normal cardiac function at baseline) using MRI indicate that treatment with EXJADE 10-30 mg/kg/day for 1 year may also reduce levels of iron in the heart (on average, MRI T2* increased from 18.3 to 23.0 milliseconds).

The principal analysis of the pivotal comparative study in 586 patients suffering from beta-thalassaemia and transfusional iron overload did not demonstrate non-inferiority of EXJADE to deferoxamine in the analysis of the total patient population. It appeared from a post-hoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with EXJADE (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron concentration <7 mg Fe/g dw treated with EXJADE (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established due to imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol specified dose. Fifty-six patients under the age of 6 years participated in this pivotal study, 28 of them receiving EXJADE.

It appeared from preclinical and clinical studies that EXJADE could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e. a dose of EXJADE that is numerically half of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical trials.

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, EXJADE up to 20 and 30 mg/kg produced a decrease in liver iron concentration and serum ferritin comparable to that obtained in patients with beta-thalassaemia.

5.2 Pharmacokinetic properties

Absorption
Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from EXJADE 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.

Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres 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*.

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. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

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.

Characteristics in patients

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

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

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.

Tests of genotoxicity *in vitro* were either negative (Ames test, chromosomal aberration test) or positive (V79 screen). Deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

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 type A
Cellulose, microcrystalline
Povidone
Sodium lauryl sulphate
Silica, colloidal anhydrous
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 in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blisters.

Packs containing 28 or 84 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/001
EU/1/06/356/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.08.2006

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 250 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 250 mg deferasirox.

This product contains lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 250 on the other).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).

4.2 Posology and method of administration

Treatment with EXJADE should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions. It is recommended that treatment 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 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

Deleted: EXJADE is available in three tablet strengths (125 mg, 250 mg and 500 mg).

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 who require reduction of elevated body iron levels and who are also 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 who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

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). When this results in a daily dose less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

Maintenance dose
It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Doses above 30 mg/kg are not recommended because there is only limited experience with doses above this level. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Preparation
EXJADE must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day (see sections 4.5 and 5.2). The tablets are dispersed by stirring in a glass of water or orange or apple juice (100 to 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 also section 6.2).

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above.

Paediatric patients (2 to 17 years of age)
The dosing recommendations for paediatric patients are the same as for adult patients. Changes in weight of paediatric patients over time must be taken into account when calculating the dose. In children aged between 2 and 5 years, exposure is lower than in adults (see section 5.2). This age group may therefore require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, followed by individual titration.

Patients with renal impairment
EXJADE has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min (see sections 4.3 and 4.4).

Patients with hepatic impairment
EXJADE has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as described above. Hepatic function in all patients should be monitored before treatment then every month (see section 4.4).

4.3 Contraindications

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

Combination with other iron chelator therapies as the safety of such combinations has not been established (see section 4.5).

Patients with estimated creatinine clearance <60 ml/min.

4.4 Special warnings and precautions for use

Renal function:

EXJADE has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Cases of acute renal failure have been reported following post-marketing use of EXJADE (see section 4.8).

The causes of the rises in serum creatinine have not been elucidated. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are receiving high doses of EXJADE and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult).

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, creatinine clearance** (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels **should be monitored weekly in the first month after initiation or modification of therapy with EXJADE, and monthly thereafter**. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting.

For adult patients, the daily dose may be reduced by 10 mg/kg if a rise in serum creatinine by >33% above the average of the pre-treatment measurements and estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) are seen at two consecutive visits, and cannot be attributed to other causes (see section 4.2). For paediatric patients, the dose may be reduced by 10 mg/kg if estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) and/or serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

After a dose reduction, for adult and paediatric patients, treatment should be interrupted if a rise in serum creatinine >33% above the average of the pre-treatment measurements is observed and/or the calculated creatinine clearance falls below the lower limit of the normal range. Treatment may be reinitiated depending on the individual clinical circumstances.

Particular attention should also be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function.

Tests for proteinuria should be performed monthly. As needed, additional markers of renal tubular function (e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria) may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

If, despite dose reduction and interruption, the serum creatinine remains significantly elevated and there is also persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome), the patient should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered.

Hepatic function:

Liver function test elevations have been observed in patients treated with EXJADE. Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with EXJADE. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However,

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EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).¶

the role of EXJADE as a contributing or aggravating factor cannot be excluded.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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 can not be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

Deleted: liver function tests be performed every month

Deleted: treatment

EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving EXJADE. Multiple ulcers have been observed in some patients (see section 4.8). Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal 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 Section 4.5 Interaction with other medicinal products and other forms of interaction).

Skin rashes may appear during EXJADE treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration.

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 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported (see section 4.8). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy (see section 4.2). If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends. The results should also be noted in the provided patient's booklet.

In the 1-year clinical studies growth and sexual development of paediatric patients treated with EXJADE were not affected. However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored at regular intervals (every 12 months).

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE.

The tablets contain lactose (1.1 mg lactose for each mg of deferasirox). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

The concomitant use of deferasirox with aluminium-containing antacid preparations is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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, it is not recommended to take EXJADE tablets with aluminium-containing antacid preparations (see section 4.4).

The bioavailability of deferasirox 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 sections 4.2 and 5.2).

Deferasirox metabolism depends on UGT enzymes. A decrease of its plasma concentration cannot be excluded when it is given with potent UGT inducers such as rifampicin, phenobarbital or phenytoin. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

In a healthy volunteer study, the concomitant administration of EXJADE and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17% (90% 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, bepridil, ergotamine).

The safety of EXJADE in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies (see section 4.3).

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

An interaction between deferasirox and CYP2C8 substrates like paclitaxel and repaglinide cannot be excluded.

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 administration of EXJADE and substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids, or oral bisphosphonates, as well as anticoagulants may increase the risk of gastrointestinal toxicity (see section 4.4). EXJADE may also increase the hemorrhage risk of anticoagulants. A close clinical monitoring should be exercised when deferasirox is combined with these drugs.

4.6 Pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see section 5.3). The potential risk for humans is unknown.

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

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

Fertility
No fertility data is available for humans. In animals, no adverse effects on male or female fertility were

found (see section 5.3).

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 reaction of dizziness should exercise caution when driving or operating machinery (see section 4.8).

4.8 Undesirable effects

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. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Indeed, in some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction (see section 4.4).

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse drug reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During postmarketing experience, hepatic failure, sometimes fatal, has been reported with Exjade, especially in patients with pre-existing liver cirrhosis (see section 4.4). As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with EXJADE (see section 4.4).

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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); not known (cannot be estimated form the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Nervous system disorders		
	Common:	Headache
	Uncommon:	Dizziness
Eye disorders		
	Uncommon:	Early cataract, maculopathy
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
Renal and urinary disorders		
	Very common:	Blood creatinine increased
	Common:	Proteinuria

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	Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
	Not known	Acute renal failure[1]
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus
	Uncommon:	Pigmentation disorder
	Not known	Urticaria[1]
General disorders and administration site conditions		
	Uncommon:	Pyrexia, oedema, fatigue
Immune system disorders		
	Not known	Hypersensitivity reactions (including anaphylaxis and angioedema)[1]
Hepatobiliary disorders		
	Common:	Transaminases increased
	Uncommon:	Hepatitis, cholelithiasis
	Not known:	Hepatic failure[1]
Psychiatric disorders		
	Uncommon:	Anxiety, sleep disorder

[1] Adverse reactions reported during postmarketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

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4.9 Overdose

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

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.

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 411 adult (age ≥16 years) and 292 paediatric patients (aged 2 to <16 years) with chronic iron overload due to blood transfusions. Of the paediatric patients 52 were aged 2 to 5 years. 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).

Daily treatment at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/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. EXJADE induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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. Limited clinical data (29 patients with normal cardiac function at baseline) using MRI indicate that treatment with EXJADE 10-30 mg/kg/day for 1 year may also reduce levels of iron in the heart (on average, MRI T2* increased from 18.3 to 23.0 milliseconds).

The principal analysis of the pivotal comparative study in 586 patients suffering from beta-thalassaemia and transfusional iron overload did not demonstrate non-inferiority of EXJADE to deferoxamine in the analysis of the total patient population. It appeared from a post-hoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with EXJADE (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron concentration <7 mg Fe/g dw treated with EXJADE (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established due to imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol specified dose. Fifty-six patients under the age of 6 years participated in this pivotal study, 28 of them receiving EXJADE.

It appeared from preclinical and clinical studies that EXJADE could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e. a dose of EXJADE that is numerically half of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical trials.

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, EXJADE up to 20 and 30 mg/kg produced a decrease in liver iron concentration and serum ferritin comparable to that obtained in patients with beta-thalassaemia.

5.2 Pharmacokinetic properties

Absorption
Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from EXJADE 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.

Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres 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*.

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. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

Linearity / non-linearity
The C_{max} and $AUC_{0\text{-}24h}$ 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.

Characteristics in patients

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

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

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.

Tests of genotoxicity *in vitro* were either negative (Ames test, chromosomal aberration test) or positive (V79 screen). Deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

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 type A
Cellulose, microcrystalline
Povidone
Sodium lauryl sulphate
Silica, colloidal anhydrous
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 in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blisters.

Packs containing 28 or 84 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/003
EU/1/06/356/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.08.2006

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 500 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 500 mg deferasirox.

This product contains lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 500 on the other).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).

4.2 Posology and method of administration

Treatment with EXJADE should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions. It is recommended that treatment 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 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

Deleted: EXJADE is available in three tablet strengths (125 mg, 250 mg and 500 mg).

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 who require reduction of elevated body iron levels and who are also 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 who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

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). When this results in a daily dose less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

Maintenance dose
It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Doses above 30 mg/kg are not recommended because there is only limited experience with doses above this level. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Preparation
EXJADE must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day (see sections 4.5 and 5.2). The tablets are dispersed by stirring in a glass of water or orange or apple juice (100 to 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 also section 6.2).

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above.

Paediatric patients (2 to 17 years of age)
The dosing recommendations for paediatric patients are the same as for adult patients. Changes in weight of paediatric patients over time must be taken into account when calculating the dose. In children aged between 2 and 5 years, exposure is lower than in adults (see section 5.2). This age group may therefore require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, followed by individual titration.

Patients with renal impairment
EXJADE has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min (see sections 4.3 and 4.4).

Patients with hepatic impairment
EXJADE has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as described above. Hepatic function in all patients should be monitored before treatment then every month (see section 4.4).

4.3 Contraindications

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

Combination with other iron chelator therapies as the safety of such combinations has not been established (see section 4.5).

Patients with estimated creatinine clearance <60 ml/min.

4.4 Special warnings and precautions for use

Renal function:

EXJADE has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Cases of acute renal failure have been reported following post-marketing use of EXJADE (see section 4.8).

The causes of the rises in serum creatinine have not been elucidated. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are receiving high doses of EXJADE and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult).

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, creatinine clearance** (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels **should be monitored weekly in the first month after initiation or modification of therapy with EXJADE, and monthly thereafter**. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting.

For adult patients, the daily dose may be reduced by 10 mg/kg if a rise in serum creatinine by >33% above the average of the pre-treatment measurements and estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) are seen at two consecutive visits, and cannot be attributed to other causes (see section 4.2). For paediatric patients, the dose may be reduced by 10 mg/kg if estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) and/or serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

After a dose reduction, for adult and paediatric patients, treatment should be interrupted if a rise in serum creatinine >33% above the average of the pre-treatment measurements is observed and/or the calculated creatinine clearance falls below the lower limit of the normal range. Treatment may be reinitiated depending on the individual clinical circumstances.

Particular attention should also be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function.

Tests for proteinuria should be performed monthly. As needed, additional markers of renal tubular function (e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria) may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated.

If, despite dose reduction and interruption, the serum creatinine remains significantly elevated and there is also persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome), the patient should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered.

Hepatic function:

Liver function test elevations have been observed in patients treated with EXJADE. Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with EXJADE. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However,

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EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).¶

the role of EXJADE as a contributing or aggravating factor cannot be excluded (see Section 4.8).

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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 can not be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

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EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range (see section 5.2).

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving EXJADE. Multiple ulcers have been observed in some patients (see section 4.8). Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal 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 Section 4.5 Interaction with other medicinal products and other forms of interaction).

Skin rashes may appear during EXJADE treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration.

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 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported (see section 4.8). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy (see section 4.2). 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.

The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends. The results should also be noted in the provided patient's booklet.

In the 1-year clinical studies growth and sexual development of paediatric patients treated with EXJADE were not affected. However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored at regular intervals (every 12 months).

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE.

The tablets contain lactose (1.1 mg lactose for each mg of deferasirox). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe

lactase deficiency should not take this medicine.

The concomitant use of deferasirox with aluminium-containing antacid preparations is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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, it is not recommended to take EXJADE tablets with aluminium-containing antacid preparations (see section 4.4).

The bioavailability of deferasirox 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 sections 4.2 and 5.2).

Deferasirox metabolism depends on UGT enzymes. A decrease of its plasma concentration cannot be excluded when it is given with potent UGT inducers such as rifampicin, phenobarbital or phenytoin. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

In a healthy volunteer study, the concomitant administration of EXJADE and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17% (90% 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, bepridil, ergotamine).

The safety of EXJADE in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies (see section 4.3).

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

An interaction between deferasirox and CYP2C8 substrates like paclitaxel and repaglinide cannot be excluded.

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 administration of EXJADE and substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids, or oral bisphosphonates, as well as anticoagulants may increase the risk of gastrointestinal toxicity (see section 4.4). EXJADE may also increase the hemorrhage risk of anticoagulants. A close clinical monitoring should be exercised when deferasirox is combined with these drugs.

4.6 Pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see section 5.3). The potential risk for humans is unknown.

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

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

Fertility

No fertility data is available for humans. In animals, no adverse effects on male or female fertility were found (see section 5.3).

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 reaction of dizziness should exercise caution when driving or operating machinery (see section 4.8).

4.8 Undesirable effects

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. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Indeed, in some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction (see section 4.4).

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse drug reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During postmarketing experience, hepatic failure, sometimes fatal, has been reported with Exjade, especially in patients with pre-existing liver cirrhosis (see section 4.4). As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with EXJADE (see section 4.4).

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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); not known (cannot be estimated form the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Nervous system disorders		
	Common:	Headache
	Uncommon:	Dizziness
Eye disorders		
	Uncommon:	Early cataract, maculopathy
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
Renal and urinary disorders		

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	Very common:	Blood creatinine increased
	Common:	Proteinuria
	Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
	Not known	Acute renal failure[1]
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus
	Uncommon:	Pigmentation disorder
	Not known	Urticaria[1]
General disorders and administration site conditions		
	Uncommon:	Pyrexia, oedema, fatigue
Immune system disorders		
	Not known	Hypersensitivity reactions (including anaphylaxis and angioedema)[1]
Hepatobiliary disorders		
	Common:	Transaminases increased
	Uncommon:	Hepatitis, cholelithiasis
	Not known:	Hepatic failure[1]
Psychiatric disorders		
	Uncommon:	Anxiety, sleep disorder

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[1] Adverse reactions reported during postmarketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

4.9 Overdose

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

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.

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 411 adult (age ≥16 years) and 292 paediatric patients (aged 2 to <16 years) with chronic iron overload due to blood transfusions. Of the paediatric patients 52 were aged 2 to 5 years. 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).

Daily treatment at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and

serum ferritin was reduced by about -36 and -926 µg/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. EXJADE induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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. Limited clinical data (29 patients with normal cardiac function at baseline) using MRI indicate that treatment with EXJADE 10-30 mg/kg/day for 1 year may also reduce levels of iron in the heart (on average, MRI T2* increased from 18.3 to 23.0 milliseconds).

The principal analysis of the pivotal comparative study in 586 patients suffering from beta-thalassaemia and transfusional iron overload did not demonstrate non-inferiority of EXJADE to deferoxamine in the analysis of the total patient population. It appeared from a post-hoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with EXJADE (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron concentration <7 mg Fe/g dw treated with EXJADE (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established due to imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol specified dose. Fifty-six patients under the age of 6 years participated in this pivotal study, 28 of them receiving EXJADE.

It appeared from preclinical and clinical studies that EXJADE could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e. a dose of EXJADE that is numerically half of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical trials.

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, EXJADE up to 20 and 30 mg/kg produced a decrease in liver iron concentration and serum ferritin comparable to that obtained in patients with beta-thalassaemia.

5.2 Pharmacokinetic properties

Absorption
Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from EXJADE 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.

Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres 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*.

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. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

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.

Characteristics in patients

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

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

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.

Tests of genotoxicity *in vitro* were either negative (Ames test, chromosomal aberration test) or positive (V79 screen). Deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

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 type A
Cellulose, microcrystalline
Povidone
Sodium lauryl sulphate
Silica, colloidal anhydrous
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 in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blisters.

Packs containing 28 or 84 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/005
EU/1/06/356/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.08.2006

10. DATE OF REVISION OF THE TEXT

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Drop the tablet(s) into a glass of water, or apple or orange juice.¶
Stir until the tablet(s) dissolve completely. The liquid in the glass will look cloudy.¶
Drink everything in the glass. Then add a little water or juice to what is left in the glass and drink that too.¶
¶
Do not dissolve the tablets in fizzy drinks or milk.¶
Do not chew, break or crush the tablets.¶
Do not swallow the tablets whole.¶

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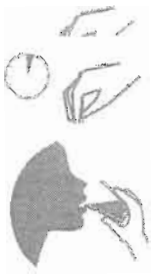

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Drop the tablet(s) into a glass of water, or apple or orange juice.
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Do not chew, break or crush the tablets.
Do not swallow the tablets whole.