

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

■ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 125 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 125 mg deferasirox.

Excipient:

Each dispersible tablet contains 136 mg lactose.

For the 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 beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) 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) aged 2 years and older,
- in patients with other anaemias aged 2 years and older.

EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

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.

Posology - transfusional iron overload

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.

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).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. The availability of long-term efficacy and safety data with EXJADE used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 30 mg/kg, a further increase (to a maximum of 40 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 30 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 30 mg/kg, dose reductions in steps of 5 to 10 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Posology - non-transfusion-dependent thalassaemia syndromes

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥ 5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 $\mu\text{g/l}$). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients.

Starting dose

The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥ 7 mg Fe/g dw, or if serum ferritin is consistently $>2,000$ $\mu\text{g/l}$ and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is $\leq 2,000$ $\mu\text{g/l}$, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is $\leq 2,000$ $\mu\text{g/l}$.

Treatment cessation

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 $\mu\text{g/l}$), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.

Special populations

Elderly patients (≥ 65 years of age)

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

Paediatric population

The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional iron overload 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 with transfusional iron overload 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.

In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤ 800 $\mu\text{g/l}$.

The safety and efficacy of EXJADE in children from birth to 23 months of age have not been established. No data are available.

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 is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50% (see sections 4.4 and 5.2), and EXJADE must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month (see section 4.4).

Method of administration

For oral use.

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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). In some post-marketing cases, renal function deterioration has led to renal failure requiring temporary or permanent dialysis.

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 concomitantly receiving medicinal products that depress renal function, and 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). While no increase in renal adverse events was observed after dose escalation to doses above 30 mg/kg in clinical trials, an increased risk of renal adverse events with EXJADE doses above 30 mg/kg cannot be excluded.

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.

There have been post-marketing reports of metabolic acidosis occurring during treatment with EXJADE. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis.

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.

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. Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

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. Post-marketing 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, 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 cannot be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Summary of safety monitoring recommendations:

Test	Frequency
Serum creatinine, creatinine clearance and/or plasma cystatin C	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Monthly
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual development	Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of EXJADE might be limited and may be inferior to risks. As a consequence, treatment with EXJADE is not recommended in these patients.

Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).

Data in children with non-transfusion-dependent thalassaemia are very limited (see section 5.1). As a consequence, EXJADE therapy should be closely monitored to detect side effects and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal

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). There have been reports of ulcers complicated with digestive perforation. Also, there have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. 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 reaction is suspected. Caution should be exercised in patients who are taking EXJADE in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm³ (50 x 10⁹/l) (see section 4.5).

Skin disorders

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 Stevens-Johnson syndrome (SJS) have been reported post marketing. The risk of other more severe skin reactions (TEN [toxic epidermal necrolysis], DRESS [drug reaction with eosinophilia and systemic symptoms]) cannot be excluded. If SJS or any other severe skin reaction is suspected, EXJADE should be discontinued immediately and should not be reintroduced.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving EXJADE, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Vision and hearing

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.

Blood disorders

There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with EXJADE. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations

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 (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), 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 one clinical study, growth and sexual development of paediatric patients treated with EXJADE for up to 5 years 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.

Each tablet contains 136 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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).

The concomitant administration of EXJADE with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity (see section 4.4). The concomitant administration of EXJADE with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

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. In a healthy volunteer study, the concomitant administration of EXJADE (single dose of 30 mg/kg) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling (see section 5.2).

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).

In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, increased repaglinide AUC and C_{max} about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]), respectively. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4). An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

In a healthy volunteer study, the concomitant administration of EXJADE as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. Therefore, the concomitant use of EXJADE with theophylline is not recommended. If EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between EXJADE and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

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.

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.

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

4.6 Fertility, 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 is not used during pregnancy unless clearly necessary.

EXJADE may decrease the efficacy of hormonal contraceptives (see section 4.5).

Breast-feeding

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

Summary of the safety profile

The most frequent reactions reported during chronic treatment with EXJADE in adult and paediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash in about 7% of patients. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly. 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 two or more 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).

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload (including patients with different characteristics such as transfusion intensity, posology and treatment duration) treated in two randomised clinical trials and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935) and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in paediatric patients was observed during the first year of treatment. In a subset of patients followed for more than one year (n=250 up to five years), no further decrease in mean creatinine clearance levels was observed in subsequent years.

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

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Blood and lymphatic system disorders	
Not known:	Pancytopenia ¹ , thrombocytopenia ¹ , anaemia aggravated ¹ , neutropenia
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylaxis and angioedema) ¹
Metabolism and nutrition disorders	
Not known:	Metabolic acidosis
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Early cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	Oesophagitis
Not known:	Gastrointestinal perforation
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure ¹

Skin and subcutaneous tissue disorders

Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Not known:	Stevens-Johnson syndrome ¹ , leukocytoclastic vasculitis ¹ , urticaria ¹ , erythema multiforme ¹ , alopecia ¹

Renal and urinary disorders

Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
Not known:	Acute renal failure ¹ , tubulointerstitial nephritis ¹ , nephrolithiasis, renal tubular necrosis ¹

General disorders and administration site conditions

Uncommon:	Pyrexia, oedema, fatigue
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¹ Adverse reactions reported during post-marketing 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.

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse 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 post-marketing experience, hepatic failure, sometimes fatal, has been reported with EXJADE, especially in patients with pre-existing liver cirrhosis (see section 4.4). There have been post-marketing reports of metabolic acidosis. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication (see section 4.4). Serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders). 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).

Paediatric population

Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients.

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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

Mechanism of action

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

Pharmacodynamic effects

In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, 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.

Clinical efficacy and safety

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 $\mu\text{g/l}$ 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.

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with EXJADE was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of matching placebo (56 patients). The study enrolled 145 adult and 21 paediatric patients. The primary efficacy parameter was the change in liver iron concentration (LIC) from baseline after 12 months of treatment. One of the secondary efficacy parameters was the change in serum ferritin between baseline and fourth quarter. At a starting dose of 10 mg/kg/day, EXJADE led to reductions in indicators of total body iron. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p < 0.001$). On average, serum ferritin decreased by 222.0 $\mu\text{g/l}$ in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 115 $\mu\text{g/l}$ in patients treated with placebo ($p < 0.001$).

The European Medicines Agency has deferred the obligation to submit the results of studies with EXJADE in one or more subsets of the paediatric population in the treatment of chronic iron overload requiring chelation therapy (see section 4.2 for information on paediatric use).

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: in a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

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 $\text{AUC}_{0-24\text{h}}$ 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 impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

In a clinical study using single doses of 20 mg/kg deferasirox, the average exposure was increased by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C) (see sections 4.2 and 4.4).

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 \pm 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 laurilsulfate
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, 84 or 252 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
EU/1/06/356/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28.08.2006

Date of latest renewal: 28.08.2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

■ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 250 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 250 mg deferasirox.

Excipient:

Each dispersible tablet contains 272 mg lactose.

For the 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 beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) 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) aged 2 years and older,
- in patients with other anaemias aged 2 years and older.

EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

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.

Posology - transfusional iron overload

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.

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).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. The availability of long-term efficacy and safety data with EXJADE used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 30 mg/kg, a further increase (to a maximum of 40 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 30 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 30 mg/kg, dose reductions in steps of 5 to 10 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Posology - non-transfusion-dependent thalassaemia syndromes

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥ 5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 $\mu\text{g/l}$). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients.

Starting dose

The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥ 7 mg Fe/g dw, or if serum ferritin is consistently $>2,000$ $\mu\text{g/l}$ and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is $\leq 2,000$ $\mu\text{g/l}$, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is $\leq 2,000$ $\mu\text{g/l}$.

Treatment cessation

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 $\mu\text{g/l}$), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.

Special populations

Elderly patients (≥ 65 years of age)

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

Paediatric population

The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional iron overload 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 with transfusional iron overload 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.

In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤ 800 $\mu\text{g/l}$.

The safety and efficacy of EXJADE in children from birth to 23 months of age have not been established. No data are available.

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 is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50% (see sections 4.4 and 5.2), and EXJADE must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month (see section 4.4).

Method of administration

For oral use.

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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). In some post-marketing cases, renal function deterioration has led to renal failure requiring temporary or permanent dialysis.

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 concomitantly receiving medicinal products that depress renal function, and 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). While no increase in renal adverse events was observed after dose escalation to doses above 30 mg/kg in clinical trials, an increased risk of renal adverse events with EXJADE doses above 30 mg/kg cannot be excluded.

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.

There have been post-marketing reports of metabolic acidosis occurring during treatment with EXJADE. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis.

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.

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. Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

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. Post-marketing 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, 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 cannot be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Summary of safety monitoring recommendations:

Test	Frequency
Serum creatinine, creatinine clearance and/or plasma cystatin C	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Monthly
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual development	Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of EXJADE might be limited and may be inferior to risks. As a consequence, treatment with EXJADE is not recommended in these patients.

Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).

Data in children with non-transfusion-dependent thalassaemia are very limited (see section 5.1). As a consequence, EXJADE therapy should be closely monitored to detect side effects and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal

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). There have been reports of ulcers complicated with digestive perforation. Also, there have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. 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 reaction is suspected. Caution should be exercised in patients who are taking EXJADE in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm³ (50 x 10⁹/l) (see section 4.5).

Skin disorders

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 Stevens-Johnson syndrome (SJS) have been reported post marketing. The risk of other more severe skin reactions (TEN [toxic epidermal necrolysis], DRESS [drug reaction with eosinophilia and systemic symptoms]) cannot be excluded. If SJS or any other severe skin reaction is suspected, EXJADE should be discontinued immediately and should not be reintroduced.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving EXJADE, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Vision and hearing

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.

Blood disorders

There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with EXJADE. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations

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 (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), 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 one clinical study, growth and sexual development of paediatric patients treated with EXJADE for up to 5 years 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.

Each tablet contains 272 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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).

The concomitant administration of EXJADE with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity (see section 4.4). The concomitant administration of EXJADE with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

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. In a healthy volunteer study, the concomitant administration of EXJADE (single dose of 30 mg/kg) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling (see section 5.2).

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).

In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, increased repaglinide AUC and C_{max} about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]), respectively. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4). An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

In a healthy volunteer study, the concomitant administration of EXJADE as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. Therefore, the concomitant use of EXJADE with theophylline is not recommended. If EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between EXJADE and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

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.

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.

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

4.6 Fertility, 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 is not used during pregnancy unless clearly necessary.

EXJADE may decrease the efficacy of hormonal contraceptives (see section 4.5).

Breast-feeding

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

Summary of the safety profile

The most frequent reactions reported during chronic treatment with EXJADE in adult and paediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash in about 7% of patients. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly. 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 two or more 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).

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload (including patients with different characteristics such as transfusion intensity, posology and treatment duration) treated in two randomised clinical trials and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935) and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in paediatric patients was observed during the first year of treatment. In a subset of patients followed for more than one year (n=250 up to five years), no further decrease in mean creatinine clearance levels was observed in subsequent years.

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

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Blood and lymphatic system disorders	
Not known:	Pancytopenia ¹ , thrombocytopenia ¹ , anaemia aggravated ¹ , neutropenia
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylaxis and angioedema) ¹
Metabolism and nutrition disorders	
Not known:	Metabolic acidosis
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Early cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	Oesophagitis
Not known:	Gastrointestinal perforation
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure ¹

Skin and subcutaneous tissue disorders

Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Not known:	Stevens-Johnson syndrome ¹ , leukocytoclastic vasculitis ¹ , urticaria ¹ , erythema multiforme ¹ , alopecia ¹

Renal and urinary disorders

Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
Not known:	Acute renal failure ¹ , tubulointerstitial nephritis ¹ , nephrolithiasis, renal tubular necrosis ¹

General disorders and administration site conditions

Uncommon:	Pyrexia, oedema, fatigue
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Adverse reactions reported during post-marketing 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.

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse 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 post-marketing experience, hepatic failure, sometimes fatal, has been reported with EXJADE, especially in patients with pre-existing liver cirrhosis (see section 4.4). There have been post-marketing reports of metabolic acidosis. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication (see section 4.4). Serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders). 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).

Paediatric population

Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients.

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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

Mechanism of action

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

Pharmacodynamic effects

In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, 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.

Clinical efficacy and safety

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 $\mu\text{g/l}$ 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.

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with EXJADE was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of matching placebo (56 patients). The study enrolled 145 adult and 21 paediatric patients. The primary efficacy parameter was the change in liver iron concentration (LIC) from baseline after 12 months of treatment. One of the secondary efficacy parameters was the change in serum ferritin between baseline and fourth quarter. At a starting dose of 10 mg/kg/day, EXJADE led to reductions in indicators of total body iron. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p < 0.001$). On average, serum ferritin decreased by 222.0 $\mu\text{g/l}$ in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 115 $\mu\text{g/l}$ in patients treated with placebo ($p < 0.001$).

The European Medicines Agency has deferred the obligation to submit the results of studies with EXJADE in one or more subsets of the paediatric population in the treatment of chronic iron overload requiring chelation therapy (see section 4.2 for information on paediatric use).

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: in a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

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 $\text{AUC}_{0-24\text{h}}$ 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 impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

In a clinical study using single doses of 20 mg/kg deferasirox, the average exposure was increased by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C) (see sections 4.2 and 4.4).

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 \pm 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 laurilsulfate
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, 84 or 252 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
EU/1/06/356/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28.08.2006

Date of latest renewal: 28.08.2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

■ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 500 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 500 mg deferasirox.

Excipient:

Each dispersible tablet contains 544 mg lactose.

For the 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 beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) 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) aged 2 years and older,
- in patients with other anaemias aged 2 years and older.

EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

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.

Posology - transfusional iron overload

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.

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).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. The availability of long-term efficacy and safety data with EXJADE used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 30 mg/kg, a further increase (to a maximum of 40 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 30 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 30 mg/kg, dose reductions in steps of 5 to 10 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Posology - non-transfusion-dependent thalassaemia syndromes

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥ 5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 $\mu\text{g/l}$). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients.

Starting dose

The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥ 7 mg Fe/g dw, or if serum ferritin is consistently $>2,000$ $\mu\text{g/l}$ and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is $\leq 2,000$ $\mu\text{g/l}$, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is $\leq 2,000$ $\mu\text{g/l}$.

Treatment cessation

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 $\mu\text{g/l}$), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.

Special populations

Elderly patients (≥ 65 years of age)

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

Paediatric population

The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional iron overload 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 with transfusional iron overload 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.

In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤ 800 $\mu\text{g/l}$.

The safety and efficacy of EXJADE in children from birth to 23 months of age have not been established. No data are available.

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 is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50% (see sections 4.4 and 5.2), and EXJADE must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month (see section 4.4).

Method of administration

For oral use.

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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). In some post-marketing cases, renal function deterioration has led to renal failure requiring temporary or permanent dialysis.

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 concomitantly receiving medicinal products that depress renal function, and 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). While no increase in renal adverse events was observed after dose escalation to doses above 30 mg/kg in clinical trials, an increased risk of renal adverse events with EXJADE doses above 30 mg/kg cannot be excluded.

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.

There have been post-marketing reports of metabolic acidosis occurring during treatment with EXJADE. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis.

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.

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. Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

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. Post-marketing 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, 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 cannot be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Summary of safety monitoring recommendations:

Test	Frequency
Serum creatinine, creatinine clearance and/or plasma cystatin C	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Monthly
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual development	Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of EXJADE might be limited and may be inferior to risks. As a consequence, treatment with EXJADE is not recommended in these patients.

Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).

Data in children with non-transfusion-dependent thalassaemia are very limited (see section 5.1). As a consequence, EXJADE therapy should be closely monitored to detect side effects and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal

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). There have been reports of ulcers complicated with digestive perforation. Also, there have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. 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 reaction is suspected. Caution should be exercised in patients who are taking EXJADE in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm³ (50 x 10⁹/l) (see section 4.5).

Skin disorders

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 Stevens-Johnson syndrome (SJS) have been reported post marketing. The risk of other more severe skin reactions (TEN [toxic epidermal necrolysis], DRESS [drug reaction with eosinophilia and systemic symptoms]) cannot be excluded. If SJS or any other severe skin reaction is suspected, EXJADE should be discontinued immediately and should not be reintroduced.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving EXJADE, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted.

Vision and hearing

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.

Blood disorders

There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with EXJADE. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations

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 (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), 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 one clinical study, growth and sexual development of paediatric patients treated with EXJADE for up to 5 years 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.

Each tablet contains 544 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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).

The concomitant administration of EXJADE with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity (see section 4.4). The concomitant administration of EXJADE with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

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. In a healthy volunteer study, the concomitant administration of EXJADE (single dose of 30 mg/kg) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling (see section 5.2).

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).

In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, increased repaglinide AUC and C_{max} about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]), respectively. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4). An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

In a healthy volunteer study, the concomitant administration of EXJADE as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. Therefore, the concomitant use of EXJADE with theophylline is not recommended. If EXJADE and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between EXJADE and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

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.

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.

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

4.6 Fertility, 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 is not used during pregnancy unless clearly necessary.

EXJADE may decrease the efficacy of hormonal contraceptives (see section 4.5).

Breast-feeding

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

Summary of the safety profile

The most frequent reactions reported during chronic treatment with EXJADE in adult and paediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash in about 7% of patients. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly. 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 two or more 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).

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload (including patients with different characteristics such as transfusion intensity, posology and treatment duration) treated in two randomised clinical trials and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935) and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in paediatric patients was observed during the first year of treatment. In a subset of patients followed for more than one year (n=250 up to five years), no further decrease in mean creatinine clearance levels was observed in subsequent years.

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

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Blood and lymphatic system disorders	
Not known:	Pancytopenia ¹ , thrombocytopenia ¹ , anaemia aggravated ¹ , neutropenia
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylaxis and angioedema) ¹
Metabolism and nutrition disorders	
Not known:	Metabolic acidosis
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Early cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	Oesophagitis
Not known:	Gastrointestinal perforation
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure ¹

Skin and subcutaneous tissue disorders

Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Not known:	Stevens-Johnson syndrome ¹ , leukocytoclastic vasculitis ¹ , urticaria ¹ , erythema multiforme ¹ , alopecia ¹

Renal and urinary disorders

Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
Not known:	Acute renal failure ¹ , tubulointerstitial nephritis ¹ , nephrolithiasis, renal tubular necrosis ¹

General disorders and administration site conditions

Uncommon:	Pyrexia, oedema, fatigue
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¹ Adverse reactions reported during post-marketing 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.

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse 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 post-marketing experience, hepatic failure, sometimes fatal, has been reported with EXJADE, especially in patients with pre-existing liver cirrhosis (see section 4.4). There have been post-marketing reports of metabolic acidosis. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication (see section 4.4). Serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders). 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).

Paediatric population

Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients.

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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

Mechanism of action

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

Pharmacodynamic effects

In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, 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.

Clinical efficacy and safety

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 $\mu\text{g/l}$ 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.

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with EXJADE was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of matching placebo (56 patients). The study enrolled 145 adult and 21 paediatric patients. The primary efficacy parameter was the change in liver iron concentration (LIC) from baseline after 12 months of treatment. One of the secondary efficacy parameters was the change in serum ferritin between baseline and fourth quarter. At a starting dose of 10 mg/kg/day, EXJADE led to reductions in indicators of total body iron. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p < 0.001$). On average, serum ferritin decreased by 222.0 $\mu\text{g/l}$ in patients treated with EXJADE (starting dose 10 mg/kg/day) and increased by 115 $\mu\text{g/l}$ in patients treated with placebo ($p < 0.001$).

The European Medicines Agency has deferred the obligation to submit the results of studies with EXJADE in one or more subsets of the paediatric population in the treatment of chronic iron overload requiring chelation therapy (see section 4.2 for information on paediatric use).

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: in a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

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 $\text{AUC}_{0-24\text{h}}$ 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 impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

In a clinical study using single doses of 20 mg/kg deferasirox, the average exposure was increased by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C) (see sections 4.2 and 4.4).

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 \pm 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 laurilsulfate
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, 84 or 252 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
EU/1/06/356/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28.08.2006

Date of latest renewal: 28.08.2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

The MAH must inform the European Medicines Agency and the CHMP of the status and results of the surveillance programme in each Member State within 6 months of the Decision and at each update of the EU Risk Management Plan.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the above reports:

- Increase in hepatic enzymes >10x ULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

The MAH must ensure that, at launch, all physicians who are expected to prescribe Exjade are provided with a physician information pack containing the following:

Product information

Physician information about Exjade (brochure and pocket card)

Patient information pack

The physician information about Exjade should contain the following key elements:

- The need to monitor serum ferritin monthly
- That Exjade causes rises in serum creatinine in some patients
 - The need to monitor serum creatinine
 - On two occasions prior to initiation of treatment
 - Every week during the first month of initiation of treatment or after therapy modification
 - Monthly thereafter
 - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
 - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)
 - Paediatrics: either >ULN or creatinine clearance falls to <LLN at two consecutive visits.
 - The need to interrupt treatment after a dose reduction if serum creatinine rises:
 - Adults and Paediatrics: remain >33% above baseline or creatinine clearance <LLN (90 ml/min)
 - The need to consider renal biopsy:
 - When serum creatinine is elevated and if another abnormality has been detected (eg. proteinuria, signs of Fanconi's Syndrome).
- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases occur in patients treated with Exjade
 - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
 - Not to prescribe to patients with pre-existing severe hepatic disease
 - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing
- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment	
Serum creatinine at Day - X	Value 1
Serum creatinine at Day - Y	Value 2

X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- The educational programme should prompt doctors to report serious ADRs and certain selected ADRs as below:
 - All serious ADRs
 - Persistent and progressive increase in hepatic enzymes
 - Increase in serum creatinine levels (>33% above baseline) or clearance creatinine decrease (<90 ml/min)

- Significant changes found in auditory or ophthalmological testing
- Gallstones
- Unexpected ADRs according to the SPC.

The Patient information pack should include the following information:

- Patient information leaflet
- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur
- Patient booklet where the physician can record the results of the above along with the dose of Exjade
- Reminder card for dates of tests

The physician information for use of Exjade in patients with non-transfusion-dependent thalassaemia (NTDT) syndromes should contain the following key elements:

- Information that only one course of treatment is proposed for NTDT patients
- The recommended doses and the rules for starting treatment
- The rules for stopping when target liver iron concentration and serum ferritin are reached
- A warning to minimise the risk of over-chelation
- A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
- A warning on the currently unknown safety consequences of long-term treatment in the paediatric population and the need to detect side effects

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The MAH shall conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate, in order to assess the long-term exposure and safety, based on a CHMP-agreed protocol.	June 2021 (final study report)

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 125 mg dispersible tablets
Deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 125 mg of deferasirox.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.
Take this medicine on an empty stomach.
Disperse tablets in water or fruit juice before swallowing. Do not swallow whole or chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/001	28 dispersible tablets
EU/1/06/356/002	84 dispersible tablets
EU/1/06/356/007	252 dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

EXJADE 125 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 125 mg dispersible tablets
Deferasirox

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 250 mg dispersible tablets
Deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 250 mg of deferasirox.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.
Take this medicine on an empty stomach.
Disperse tablets in water or fruit juice before swallowing. Do not swallow whole or chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/003	28 dispersible tablets
EU/1/06/356/004	84 dispersible tablets
EU/1/06/356/008	252 dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

EXJADE 250 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 250 mg dispersible tablets
Deferasirox

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 500 mg dispersible tablets
Deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 500 mg of deferasirox.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.
Take this medicine on an empty stomach.
Disperse tablets in water or fruit juice before swallowing. Do not swallow whole or chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/005	28 dispersible tablets
EU/1/06/356/006	84 dispersible tablets
EU/1/06/356/009	252 dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

EXJADE 500 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 500 mg dispersible tablets
Deferasirox

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EXJADE 125 mg dispersible tablets

EXJADE 250 mg dispersible tablets

EXJADE 500 mg dispersible tablets

Deferasirox

■ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed only for you or your child. Do not give it to anyone else or use it for any other illnesses.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EXJADE is and what it is used for
2. What you need to know before you take EXJADE
3. How to take EXJADE
4. Possible side effects
5. How to store EXJADE
6. Contents of the pack and other information

1. What EXJADE is and what it is used for

What EXJADE is

EXJADE contains an active substance called deferasirox. It is an iron chelator which is a medicine used to remove the excess iron from the body (also called iron overload).

What EXJADE is used for

Repeated blood transfusions may be necessary in patients with various types of anaemia (for example thalassaemia, sickle cell disease or myelodysplastic syndromes). However, repeated blood transfusions can cause a build-up of excess iron. This is because blood contains iron and your body does not have a natural way to remove the excess iron you get with your blood transfusions. In patients with non-transfusion-dependent thalassaemia syndromes, iron overload may also develop over time, mainly due to increased absorption of dietary iron in response to low blood cell counts. Over time, the excess iron can damage important organs such as the liver and heart. Medicines called *iron chelators* are used to remove the excess iron and reduce the risk of it causing organ damage.

EXJADE is used to treat chronic iron overload caused by frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also used to treat chronic iron overload when deferoxamine therapy is contraindicated or inadequate in patients with beta thalassaemia major with iron overload caused by infrequent blood transfusions, in patients with other types of anaemias, and in children aged 2 to 5 years.

EXJADE is also used when deferoxamine therapy is contraindicated or inadequate to treat patients aged 10 years or older who have iron overload associated with their thalassaemia syndromes, but who are not transfusion dependent.

How EXJADE works

EXJADE traps and removes excess iron which is then excreted mainly in the stools.

2. What you need to know before you take EXJADE

Follow all the doctor's instructions carefully. They may differ from the general information in this leaflet.

Do not take EXJADE

- if you are allergic to deferasirox or any of the other ingredients of this medicine (listed in section 6). If this applies to you, **tell your doctor before taking EXJADE**. If you think you may be allergic, ask your doctor for advice.
- if you have moderate or severe kidney disease.
- if you are currently taking another iron chelator medication.

EXJADE is not recommended

- if you are at an advanced stage of myelodysplastic syndrome (MDS; decreased production of blood cells by the bone marrow) or have advanced cancer.

Warnings and precautions

Talk to your doctor or pharmacist before taking EXJADE

- if you have a kidney or liver problem.
- if you have a cardiac problem due to iron overload.
- if you notice a marked decrease in your urine output (sign of kidney problem).
- if you develop a severe rash, or difficulty breathing and dizziness or swelling mainly of the face and throat (signs of severe allergic reaction, see also section 4 "Possible side effects").
- if you develop a rash, reddening of the skin, blistering of lips, eyes or mouth, skin peeling, sore throat (signs of severe skin reaction, see also section 4 "Possible side effects").
- if you experience a combination of drowsiness, upper right abdominal pain, yellowing or increased yellowing of your skin or eyes and dark urine (signs of liver problems).
- if you vomit blood and/or have black stools.
- if you experience frequent abdominal pain, particularly after eating or taking EXJADE.
- if you experience frequent heartburn.
- if you have a low level of platelets or white blood cells in your blood test.
- if you have blurred vision or vomiting.
- if you have diarrhoea or vomiting.

If any of these apply to you, tell your doctor straight away.

Monitoring your EXJADE treatment

You will have regular blood and urine tests during treatment. These will monitor the amount of iron in your body (blood level of *ferritin*) to see how well EXJADE is working. The tests will also monitor your kidney function (blood level of creatinine, presence of protein in the urine) and liver function (blood level of transaminases). You may also have MRI (magnetic resonance imaging) tests to determine the amount of iron in your liver. Your doctor will take these tests into consideration when deciding on the dose of EXJADE most suitable for you and will also use these tests to decide when you should stop taking EXJADE.

You will get a booklet from your doctor which will help you to track your response to EXJADE. Your doctor will write your blood tests in this booklet at each visit. Keep the booklet safe and bring it with you each time you visit your doctor.

Your eyesight and hearing will be tested each year during treatment as a precautionary measure.

Other medicines and EXJADE

EXJADE must not be taken with other iron chelators.

Antacids (medicines used to treat heartburn) containing aluminium should not be taken at the same time of day as EXJADE.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:

- ciclosporin (used to prevent the body rejecting a transplanted organ or for other conditions, such as rheumatoid arthritis or atopic dermatitis),
- simvastatin (used to lower cholesterol),
- certain painkillers or anti-inflammatory medicines (e.g. aspirin, ibuprofen, corticosteroids),
- oral bisphosphonates (used to treat osteoporosis),
- anticoagulant medicines (used to prevent or treat blood clotting),
- hormonal contraceptive agents (birth control medicines),
- bepridil, ergotamine,
- repaglinide (used to treat diabetes),
- rifampicin (used to treat tuberculosis),
- phenytoin, phenobarbital, carbamazepine (used to treat epilepsy),
- ritonavir (used in the treatment of HIV infection),
- paclitaxel (used in cancer treatment),
- theophylline (used to treat respiratory diseases such as asthma),
- clozapine (used to treat psychiatric disorders such as schizophrenia),
- tizanidine (used as a muscle relaxant),
- cholestyramine (used to lower cholesterol levels in the blood).

Additional tests may be required to monitor the blood levels of some of these medicines.

Older people (age 65 years and over)

EXJADE can be used by people aged 65 years and over at the same dose as for other adults. Elderly patients may experience more side effects (in particular diarrhoea) than younger patients. They should be monitored closely by their doctor for side effects that may require a dose adjustment.

Children and adolescents (age 2 years to 17 years)

EXJADE can be used in adolescents and children receiving regular blood transfusions aged 2 years and over and in adolescents and children not receiving regular blood transfusions aged 10 years and over. As the patient grows the doctor will adjust the dose.

Pregnancy and breast-feeding

EXJADE is not recommended during pregnancy unless clearly necessary. If you are pregnant or think that you may be, tell your doctor who will discuss with you whether you can take EXJADE during your pregnancy.

Breast-feeding is not recommended during treatment with EXJADE. Tell your doctor if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

If you feel dizzy after taking EXJADE, do not drive or operate any tools or machines until you are feeling normal again.

EXJADE contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take EXJADE

Treatment with EXJADE will be overseen by a doctor who is experienced in the treatment of iron overload caused by blood transfusions.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much EXJADE to take

The dose of EXJADE is related to body weight for all patients. Your doctor will calculate the dose you need and tell you how many tablets to take each day.

- The usual daily dose at the start of the treatment is 20 mg per kilogram body weight for patients receiving regular blood transfusions. A higher or lower starting dose may be recommended by your doctor based on your individual treatment needs.
- The usual daily dose at the start of the treatment for patients not receiving regular blood transfusions is 10 mg per kilogram body weight.
- Depending on how you respond to treatment, your doctor may later adjust your treatment to a higher or lower dose.
- The maximum recommended daily dose is 40 mg per kilogram body weight for patients receiving regular blood transfusions, 20 mg per kilogram body weight for adult patients not receiving regular blood transfusions and 10 mg per kilogram body weight for paediatric patients not receiving regular blood transfusions.

When to take EXJADE

- Take EXJADE once a day, every day, at about the same time each day.
- Take the tablets on an empty stomach.
- Then wait at least 30 minutes before eating any food.

Taking EXJADE at the same time each day will also help you remember when to take your tablets.

How to take EXJADE:

- **Drop** the tablet(s) into a glass of water, or apple or orange juice (100 to 200 ml).
- **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, swirl the liquid around 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.



How long to take EXJADE

Continue taking EXJADE every day for as long as your doctor tells you. This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect (see also section 2: “Monitoring your EXJADE treatment”).

If you have questions about how long to take EXJADE, talk to your doctor.

If you take more EXJADE than you should

If you have taken too much EXJADE, or if someone else accidentally takes your tablets, contact your doctor or hospital for advice straight away. Show them the pack of tablets. Medical treatment may be necessary.

If you forget to take EXJADE

If you miss a dose, take it as soon as you remember on that day. Take your next dose as scheduled. Do not take a double dose on the next day to make up for the forgotten tablet(s).

If you stop taking EXJADE

Do not stop taking EXJADE unless your doctor tells you to. If you stop taking it, the excess iron will no longer be removed from your body (see also above section “How long to take EXJADE”).

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Some side effects could be serious and need immediate medical attention.

These side effects are uncommon or rare.

- If you get a severe rash, or difficulty breathing and dizziness or swelling mainly of the face and throat (signs of severe allergic reaction),
- If you get a severe rash, reddening of the skin, blistering of lips, eyes or mouth, skin peeling, sore throat (signs of severe skin reaction),
- If you notice a marked decrease in your urine output (sign of kidney problem),
- If you experience a combination of drowsiness, upper right abdominal pain, yellowing or increased yellowing of your skin or eyes and dark urine (signs of liver problems),
- If you vomit blood and/or have black stools,
- If you experience frequent abdominal pain, particularly after eating or taking EXJADE,
- If you experience frequent heartburn,
- If you experience partial loss of vision,

stop taking this medicine and tell your doctor straight away.

Some side effects could become serious.

These side effects are uncommon, that is they may affect up to 1 in 100 people.

- If you get blurred or cloudy eyesight,
- If you get reduced hearing,

tell your doctor as soon as possible.

Some side effects are very common.

These side effects may affect more than 1 in 10 people.

- Disturbance in renal function tests.

Some side effects are common.

These side effects may affect up to 1 in 10 people.

- Gastrointestinal disorders, such as nausea, vomiting, diarrhoea, pain in the abdomen, bloating, constipation, indigestion
- Rash
- Headache
- Disturbance in liver function tests
- Itching

- Disturbance in urine test (protein in the urine)

If any of these affects you severely, tell your doctor.

Other side effects are uncommon.

These side effects may affect up to 1 in 100 people.

- Dizziness
- Fever
- Sore throat
- Swelling of arms or legs
- Change in the colour of the skin
- Anxiety
- Sleep disorder
- Tiredness

If any of these affects you severely, tell your doctor.

Frequency not known (cannot be estimated from the available data).

- A decrease in the number of cells involved in blood clotting (thrombocytopenia), in the number of red blood cells (anaemia aggravated), in the number of white blood cells (neutropenia) or in the number of all kinds of blood cells (pancytopenia)
- Hair loss
- Kidney stones
- Low urine output
- Formation of a hole in the stomach or intestine
- Abnormal level of acid in blood

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EXJADE

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from moisture.
- Do not use any pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What EXJADE contains

The active substance is deferasirox.

Each tablet of EXJADE 125 mg contains 125 mg deferasirox.

Each tablet of EXJADE 250 mg contains 250 mg deferasirox.

Each tablet of EXJADE 500 mg contains 500 mg deferasirox.

The other ingredients are lactose monohydrate, crospovidone type A, povidone, sodium laurilsulfate, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

What EXJADE looks like and contents of the pack

EXJADE is supplied as dispersible tablets. The tablets are off-white, round and flat. Each tablet contains 125 mg, 250 mg or 500 mg deferasirox:

- EXJADE 125 mg tablets are stamped “J 125” on one side and “NVR” on the other.
- EXJADE 250 mg tablets are stamped “J 250” on one side and “NVR” on the other.
- EXJADE 500 mg tablets are stamped “J 500” on one side and “NVR” on the other.

Each blister pack contains 28, 84 or 252 dispersible tablets.

Not all pack sizes or strengths may be available in your country.

Marketing Authorisation Holder

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO
THE TERMS OF THE MARKETING AUTHORISATION**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Exjade, the scientific conclusions of PRAC are as follows:

The PRAC continues to be strongly concerned by the renal safety profile of Exjade, particularly in paediatric patients. This risk is already addressed in the risk management plan with wording in the SmPC; the PRAC however considers that the SmPC wording should be further strengthened with the specific term “renal tubular necrosis” added to section 4.8. In addition, based on the data provided, the risk of “nephrolithiasis” should also be added to the section 4.8 of the SmPC.

In order to ensure that physicians follow the recommendations regarding the risk of gastric ulcer and digestive haemorrhage, a warning on the risk of gastrointestinal perforation should be added to section 4.4 the SmPC.

The risk of “metabolic acidosis” should be added to section 4.4 and 4.8 of the SmPC with a frequency of unknown.

Section 4.4 of the SmPC should be updated to include information on the risk of severe skin reactions in light of these being added to the RMP as an important potential risk.

During the reporting period, one new case of optic neuritis was reported. This risk is listed as an identified risk in the RMP and should be added to section 4.8 with a frequency of rare.

The PRAC recommends the addition of “neutropenia” to section 4.8 of the SmPC with a frequency of “not known” due to the significant number of cumulative events.

Therefore, in view of available data regarding deferasirox, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Exjade, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance DEFERASIROX is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.