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
EXJADE 250 mg dispersible tablets
EXJADE 500 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXJADE 125 mg dispersible tablets
Each dispersible tablet contains 125 mg deferasirox.

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

EXJADE 250 mg dispersible tablets
Each dispersible tablet contains 250 mg deferasirox.

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

EXJADE 500 mg dispersible tablets
Each dispersible tablet contains 500 mg deferasirox.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

EXJADE 125 mg dispersible tablets
Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 125 on the other). Approximate tablet dimensions 12 mm x 3.6 mm.

EXJADE 250 mg dispersible tablets
Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 250 on the other). Approximate tablet dimensions 15 mm x 4.7 mm.

EXJADE 500 mg dispersible tablets
Off-white, round, flat tablets with bevelled edges and imprints (NVR on one face and J 500 on the other). Approximate tablet dimensions 20 mm x 5.6 mm.

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 paediatric 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 adult and paediatric 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 adult and paediatric 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 (PRBC) 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.

In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40% higher than the dose of film-coated tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 1 Recommended doses for transfusional iron overload

	Film-coated tablets	Dispersible tablets	Transfusions	Serum ferritin
Starting dose	**14 mg/kg/day**	**20 mg/kg/day**	After 20 units (about 100 ml/kg) of PRBC or	>1,000 µg/l
Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)	
	7 mg/kg/day	10 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)	
For patients well managed on deferoxamine	One third of deferoxamine dose	Half of deferoxamine dose		
Monitoring				**Monthly**
Target range				**500-1,000 µg/**l
Adjustment steps (every 3-6 months)	**Increase**			>2,500 µg/l
	3.5 - 7 mg/kg/day Up to 28 mg/kg/day	5-10 mg/kg/day Up to 40 mg/kg/day		
	Decrease			
	3.5 - 7 mg/kg/day In patients treated with doses >21 mg/kg/day	5-10 mg/kg/day In patients treated with doses >30 mg/kg/day		<2,500 µg/l
	- When target is reached			500-1,000 µg/l
Maximum dose	**28 mg/kg/day**	**40 mg/kg/day**		
Consider interruption				**<500 µg/l**

Starting dose
The recommended initial daily dose of EXJADE dispersible tablets 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 dispersible tablets 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 dispersible tablets). 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 dispersible tablets 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).

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 µg/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.

In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40% higher than the dose of film-coated tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 2 Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	**10 mg/kg/day**	≥5 mg Fe/g dw	or	>800 µg/l
Monitoring					**Monthly**
Adjustment steps (every 3-6 months)	**Increase**		≥7 mg Fe/g dw	or	>2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10 mg/kg/day**			
	For adults		not assessed	and	≤2,000 µg/l
	For paediatric patients				
Interruption			**<3 mg Fe/g dw**	or	**<300 µg/l**
Retreatment			**Not recommended**		

*LIC is the preferred method of iron overload determination.

Starting dose
The recommended initial daily dose of EXJADE dispersible tablets 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 µg/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 ≤2,000 µg/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 ≤2,000 µg/l.

Treatment cessation
Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/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.

<u>*Special populations*</u>

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above. In clinical studies, 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
Transfusional iron overload:
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.

Non-transfusion-dependent thalassaemia syndromes:
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 µg/l.

Children from birth to 23 months:
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 dispersible tablets 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 dispersible 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

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

During clinical studies, 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. In some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction. Cases of acute renal failure have been reported following post-marketing use of deferasirox (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 deferasirox 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 of EXJADE dispersible tablets to doses above 30 mg/kg in clinical studies, an increased risk of renal adverse events with EXJADE dispersible tablet 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 prior to therapy, 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 deferasirox. 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.

Table 3 Dose adjustment and interruption of treatment for renal monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			**<60 ml/min**
Monitoring - First month after start of therapy or dose modification - Thereafter	 Weekly Monthly	 and and	 Weekly Monthly
Reduction of daily dose by 10 mg/kg/day (dispersible tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			
Adult patients Paediatric patients	>33% above pre-treatment average > age appropriate ULN**	and and/or	Decreases <LLN* (<90 ml/min) Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range **ULN: upper limit of the normal range			

Treatment may be reinitiated depending on the individual clinical circumstances.

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

- Proteinuria (test should be performed prior to therapy and monthly thereafter)
- Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

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

Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:

- Serum creatinine remains significantly elevated and
- Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome).

Hepatic function

Liver function test elevations have been observed in patients treated with deferasirox. Post-marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However, the role of deferasirox 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	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Prior to therapy. Monthly thereafter.
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	Prior to therapy. 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 adverse reactions 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 disorders

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. 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/mm^3 (50 x 10^9/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 deferasirox, 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. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock (see section 4.3).

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 deferasirox. 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.

In one clinical study, growth and sexual development of paediatric patients treated with deferasirox 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 prior to therapy and 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.

Lactose content
The dispersible tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The safety of deferasirox 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).

Interaction with food
The bioavailability of deferasirox was increased to a variable extent when taken along with food. EXJADE dispersible tablets 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).

Agents that may decrease EXJADE systemic exposure
Deferasirox metabolism depends on UGT enzymes. In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) 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).

Interaction with midazolam and other agents metabolised by CYP3A4
In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablets 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).

Interaction with repaglinide and other agents metabolised by CYP2C8
In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily, dispersible tablet formulation), 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.

Interaction with theophylline and other agents metabolised by CYP1A2
In a healthy volunteer study, the concomitant administration of deferasirox as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day, dispersible tablet formulation) 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 deferasirox with theophylline is not recommended. If deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox 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.

Other information
The concomitant administration of deferasirox and aluminium-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox tablets with aluminium-containing antacid preparations.

The concomitant administration of deferasirox 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 deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

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). Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using EXJADE.

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

EXJADE has minor influence on the ability to drive and use machines. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent reactions reported during chronic treatment with deferasirox dispersible tablets in adult and paediatric patients include gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash. 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 studies, dose-dependent increases in serum creatinine occurred in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been observed in both paediatric and adult patients with beta-thalassemia and iron overload during the first year of treatment, but there is evidence that this does not decrease further in subsequent years of treatment. Elevations of liver transaminases have been reported. Safety monitoring schedules for renal and liver parameters are recommended. Auditory (decreased hearing) and ocular (lens opacities) disturbances are uncommon, and yearly examinations are also recommended (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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 4

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

[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.

Description of selected adverse reactions

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 the deferasirox dispersible tablet formulation, 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 deferasirox (see section 4.4).

Creatinine clearance in transfusional iron overload

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload treated with deferasirox dispersible tablets in two randomised 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 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed.

Clinical study in patients with non-transfusion-dependent thalassaemia syndromes

In a 1-year study in patients with non-transfusion-dependent thalassaemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day), diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8% of patients, respectively. 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.

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 deferasirox.

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 of the deferasirox dispersible tablet formulation 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 agents, ATC code: V03AC03

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

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

Clinical efficacy and safety
Clinical efficacy studies were conducted with deferasirox dispersible tablets.

Deferasirox 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 with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/l on average, respectively. At these same doses the ratios of iron excretion : iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. Deferasirox induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg (dispersible tablet formulation) for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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 deferasirox 10-30 mg/kg/day (dispersible tablet formulation) 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 deferasirox dispersible tablets 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 deferasirox dispersible tablets (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 deferasirox dispersible tablets (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 deferasirox dispersible tablets.

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

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, deferasirox dispersible tablets 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 deferasirox dispersible tablets was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox dispersible tablet 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, deferasirox dispersible tablets 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 deferasirox dispersible tablets (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 µg/l in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 115 µg/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 (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) 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 $AUC_{0\text{-}24h}$ of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3.

Characteristics in patients
Paediatric patients
The overall exposure of adolescents (12 to ≤17 years) and children (2 to <12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was about 50% lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

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

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

Renal or hepatic impairment
The pharmacokinetics of deferasirox have not been studied in patients with renal 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 dispersible tablets, 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

Non-clinical data reveal no special hazard for humans, 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 negative (Ames test, chromosomal aberration test) while deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

The potential for toxicity to reproduction was assessed in rats and rabbits. Deferasirox was not teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother. Deferasirox did not cause other effects on fertility or reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Crospovidone type A
Cellulose, microcrystalline
Povidone
Sodium 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.

EXJADE 125 mg dispersible tablets
Packs containing 28, 84 or 252 dispersible tablets.

EXJADE 250 mg dispersible tablets
Packs containing 28, 84 or 252 dispersible tablets.

EXJADE 500 mg dispersible tablets
Unit packs containing 28, 84 or 252 dispersible tablets and multipacks containing 294 (3 packs of 98) 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EXJADE 125 mg dispersible tablets
EU/1/06/356/001
EU/1/06/356/002
EU/1/06/356/007

EXJADE 250 mg dispersible tablets
EU/1/06/356/003
EU/1/06/356/004
EU/1/06/356/008

EXJADE 500 mg dispersible tablets
EU/1/06/356/005
EU/1/06/356/006
EU/1/06/356/009
EU/1/06/356/010

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 medicinal 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 90 mg film-coated tablets
EXJADE 180 mg film-coated tablets
EXJADE 360 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXJADE 90 mg film-coated tablets
Each film-coated tablet contains 90 mg deferasirox.

EXJADE 180 mg film-coated tablets
Each film-coated tablet contains 180 mg deferasirox.

EXJADE 360 mg film-coated tablets
Each film-coated tablet contains 360 mg deferasirox.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

EXJADE 90 mg film-coated tablets
Light blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 90 on the other). Approximate tablet dimensions 10.7 mm x 4.2 mm.

EXJADE 180 mg film-coated tablets
Medium blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 180 on the other). Approximate tablet dimensions 14 mm x 5.5 mm.

EXJADE 360 mg film-coated tablets
Dark blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 360 on the other). Approximate tablet dimensions 17 mm x 6.7 mm.

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 paediatric 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 adult and paediatric 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 adult and paediatric 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 (PRBC) 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.

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 1 Recommended doses for transfusional iron overload

	Film-coated tablets	Dispersible tablets	Transfusions	Serum ferritin
Starting dose	**14 mg/kg/day**	**20 mg/kg/day**	After 20 units (about 100 ml/kg) of PRBC or	>1,000 µg/l
Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)	
	7 mg/kg/day	10 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)	
For patients well managed on deferoxamine	One third of deferoxamine dose	Half of deferoxamine dose		
Monitoring				**Monthly**
Target range				**500-1,000 µg/**l
Adjustment steps (every 3-6 months)	**Increase**			>2,500 µg/l
	3.5 - 7 mg/kg/day Up to 28 mg/kg/day	5-10 mg/kg/day Up to 40 mg/kg/day		
	Decrease			
	3.5 - 7 mg/kg/day In patients treated with doses >21 mg/kg/day	5-10 mg/kg/day In patients treated with doses >30 mg/kg/day		<2,500 µg/l
	- When target is reached			500-1,000 µg/l
Maximum dose	**28 mg/kg/day**	**40 mg/kg/day**		
Consider interruption				**<500 µg/l**

Starting dose
The recommended initial daily dose of EXJADE film-coated tablets is 14 mg/kg body weight.

An initial daily dose of 21 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 7 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 film-coated tablets that is numerically one third 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 14 mg/kg/day of EXJADE film-coated tablets). When this results in a daily dose less than 14 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 3.5 to 7 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 21 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 28 mg/kg may be considered. The availability of long-term efficacy and safety data with EXJADE dispersible tablets 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 21 mg/kg, a further increase (to a maximum of 28 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 21 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 21 mg/kg, dose reductions in steps of 3.5 to 7 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 3.5 to 7 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).

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 µg/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.

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 2 Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	**10 mg/kg/day**	≥5 mg Fe/g dw	or	>800 µg/l
Monitoring					**Monthly**
Adjustment steps (every 3-6 months)	**Increase**		≥7 mg Fe/g dw	or	>2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10 mg/kg/day**			
	For adults		not assessed	and	≤2,000 µg/l
	For paediatric patients				
Interruption			**<3 mg Fe/g dw**	or	**<300 µg/l**
Retreatment			**Not recommended**		

*LIC is the preferred method of iron overload determination.

Starting dose
The recommended initial daily dose of EXJADE film-coated tablets in patients with non-transfusion-dependent thalassaemia syndromes is 7 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 3.5 to 7 mg/kg should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 µg/l, dosing should not exceed 7 mg/kg.

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

Treatment cessation
Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/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.

<u>*Special populations*</u>

Elderly patients (≥65 years of age)
The dosing recommendations for elderly patients are the same as described above. In clinical studies, 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
Transfusional iron overload:
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.

Non-transfusion-dependent thalassaemia syndromes:
In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 7 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 µg/l.

Children from birth to 23 months:
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.

The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

The film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal (see sections 4.5 and 5.2).

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

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

During clinical studies, 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. In some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction. Cases of acute renal failure have been reported following post-marketing use of deferasirox (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 deferasirox 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 of EXJADE dispersible tablets to doses above 30 mg/kg in clinical studies, an increased risk of renal adverse events with film-coated tablets doses above 21 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 prior to therapy, 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 deferasirox. 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.

Table 3 Dose adjustment and interruption of treatment for renal monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			**<60 ml/min**
Monitoring - First month after start of therapy or dose modification - Thereafter	 Weekly Monthly	 and and	 Weekly Monthly
Reduction of daily dose by 7 mg/kg/day (film-coated tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			
Adult patients Paediatric patients	>33% above pre-treatment average > age appropriate ULN**	and and/or	Decreases <LLN* (<90 ml/min) Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range **ULN: upper limit of the normal range			

Treatment may be reinitiated depending on the individual clinical circumstances.

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

- Proteinuria (test should be performed prior to therapy and monthly thereafter)
- Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

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

Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:

- Serum creatinine remains significantly elevated and
- Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome).

Hepatic function

Liver function test elevations have been observed in patients treated with deferasirox. Post-marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However, the role of deferasirox 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	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Prior to therapy. Monthly thereafter.
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	Prior to therapy. 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 adverse reactions 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 disorders

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. 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/mm^3 (50 x 10^9/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 deferasirox, 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. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock (see section 4.3).

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 deferasirox. 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.

In one clinical study, growth and sexual development of paediatric patients treated with deferasirox 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 prior to therapy and 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.

4.5 Interaction with other medicinal products and other forms of interaction

The safety of deferasirox 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).

Interaction with food
The C_{max} of deferasirox film-coated tablets was increased (by 29%) when taken with a high-fat meal. EXJADE film-coated tablets may be taken either on an empty stomach or with a light meal, preferably at the same time each day (see sections 4.2 and 5.2).

Agents that may decrease EXJADE systemic exposure
Deferasirox metabolism depends on UGT enzymes. In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) 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).

Interaction with midazolam and other agents metabolised by CYP3A4
In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablets 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).

Interaction with repaglinide and other agents metabolised by CYP2C8
In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily, dispersible tablet formulation), 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.

Interaction with theophylline and other agents metabolised by CYP1A2
In a healthy volunteer study, the concomitant administration of deferasirox as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day, dispersible tablet formulation) 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 deferasirox with theophylline is not recommended. If deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox 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.

Other information
The concomitant administration of deferasirox and aluminium-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox tablets with aluminium-containing antacid preparations.

The concomitant administration of deferasirox 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 deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

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). Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using EXJADE.

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

EXJADE has minor influence on the ability to drive and use machines. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent reactions reported during chronic treatment with deferasirox dispersible tablets in adult and paediatric patients include gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash. 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 studies dose-dependent increases in serum creatinine occurred in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been observed in both paediatric and adult patients with beta-thalassemia and iron overload during the first year of treatment, but there is evidence that this does not decrease further in subsequent years of treatment. Elevations of liver transaminases have been reported. Safety monitoring schedules for renal and liver parameters are recommended. Auditory (decreased hearing) and ocular (lens opacities) disturbances are uncommon, and yearly examinations are also recommended (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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 4

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

[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.

Description of selected adverse reactions

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 the deferasirox dispersible tablet formulation, 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 deferasirox (see section 4.4).

Creatinine clearance in transfusional iron overload

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload treated with deferasirox dispersible tablets in two randomised 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 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed.

Clinical study in patients with non-transfusion-dependent thalassaemia syndromes

In a 1-year study in patients with non-transfusion-dependent thalassaemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day), diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8% of patients, respectively. 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.

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 deferasirox.

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 of the deferasirox dispersible tablet formulation (corresponding to a dose of 56 mg/kg film-coated tablets) 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 agents, ATC code: V03AC03

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

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

Clinical efficacy and safety
Clinical efficacy studies were conducted with deferasirox dispersible tablets.

Deferasirox 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 with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/l on average, respectively. At these same doses the ratios of iron excretion : iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. Deferasirox induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg (dispersible tablet formulation)for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. 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 deferasirox 10-30 mg/kg/day (dispersible tablet formulation) 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 deferasirox dispersible tablets 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 deferasirox dispersible tablets (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 deferasirox dispersible tablets (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 deferasirox dispersible tablets.

It appeared from preclinical and clinical studies that deferasirox dispersible tablets could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e. a dose of deferasirox dispersible tablets that is numerically half of the deferoxamine dose). For deferasirox film-coated tablets, a dose ratio of 3:1 can be considered (i.e. a dose of deferasirox film-coated tablets that is numerically one third of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical studies.

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, deferasirox dispersible tablets 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 deferasirox dispersible tablets was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox dispersible tablet 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, deferasirox dispersible tablets 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 deferasirox dispersible tablets (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 µg/l in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 115 µg/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

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation. After adjustment of the strength, the film-coated tablet formulation (360 mg strength) was equivalent to EXJADE dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase.

Absorption
Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) is about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been determined. Bioavailability of deferasirox film-coated tablets was 36% greater than that with dispersible tablets.

A food-effect study involving administration of the film-coated tablets to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased (by 18% and 29%, respectively). The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that the film-coated tablets should be taken either on an empty stomach or with a light meal.

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 $AUC_{0\text{-}24h}$ of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3.

Characteristics in patients
Paediatric patients
The overall exposure of adolescents (12 to ≤17 years) and children (2 to <12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was about 50% lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

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

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

Renal or hepatic impairment
The pharmacokinetics of deferasirox have not been studied in patients with renal 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 dispersible tablets, 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

Non-clinical data reveal no special hazard for humans, 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 negative (Ames test, chromosomal aberration test) while deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

The potential for toxicity to reproduction was assessed in rats and rabbits. Deferasirox was not teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother. Deferasirox did not cause other effects on fertility or reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Crospovidone
Povidone (K30)
Magnesium stearate
Silica, colloidal anhydrous
Poloxamer 188

Coating material:
Hypromellose
Titanium dioxide (E171)
Macrogol (4000)
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters.

Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EXJADE 90 mg film-coated tablets
EU/1/06/356/011
EU/1/06/356/012
EU/1/06/356/013

EXJADE 180 mg film-coated tablets
EU/1/06/356/014
EU/1/06/356/015
EU/1/06/356/016

EXJADE 360 mg film-coated tablets
EU/1/06/356/017
EU/1/06/356/018
EU/1/06/356/019

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 medicinal 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and and any subsequent updates 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.

- **Additional risk minimisation measures**

The MAH must inform the European Medicines Agency and the CHMP of the results of the surveillance programme in each Member State.

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

Prior to launch of EXJADE in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to inform healthcare professionals and patients to minimise the risks of:

- Non-compliance of the posology and biological monitoring
- Medication errors due to switching between formulations (dispersible and film-coated tablets).

The MAH shall ensure that, at launch, in each Member State where EXJADE is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use EXJADE are provided with the following educational package for both formulations and on all indications:

- Physician educational material
- Patient information pack

Additional periodic distributions after launch should be performed, notably after safety substantial product information modifications justifying educational material updates.

The MAH shall use distinct outer cartons, blisters and tablets for both formulations (dispersible and film-coated tablet).

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- Description of available deferasirox formulations
    - Different posology regimen
    - Different conditions of administration
    - Dose conversion table when switching from one formulation to another
- The recommended doses and the rules for starting treatment
- The need to monitor serum ferritin monthly

- That deferasirox 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 (e.g. 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 may 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.

- Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes:
    - 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

Prior to launch of deferasirox film-coated tablets, healthcare professionals will receive introductory notification letters as follows:

- Pharmacists - a detailed letter explaining the switch between the two formulations
- Prescribers - a letter including the following dossiers:
    - A prescribers' guide informing about the switch between the two formulations in order to address the important potential risk of medication error for deferasirox
    - A patient's guide informing about the possibility of two co-existing formulations in the EU market, and the differences concerning their administration, in order to address the important potential risk of medication error for deferasirox

Additionally, prescribers and pharmacists will be informed via a specific letter regarding the timelines for removing EXJADE dispersible tablets from the EU market.

The patient information pack should contain:

- Patient information leaflet
- Patient guide

Patient guide should contain the following key elements:

- 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
- Availability of several oral formulations and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food)

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

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

Description	**Due date**
The MAH shall submit the results of a Phase II safety study investigating the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet.	September 2016 (final study report)
Non-interventional post-authorisation safety study (PASS): In order to assess the long-term exposure and safety of deferasirox dispersible and film-coated tablets, the MAH should conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate conducted according to a CHMP-agreed protocol. The clinical study report should be submitted by	June 2021
Interventional post-authorisation safety study (PASS): In order to assess the safety of deferasirox film-coated tablets in the paediatric population (especially when the tablets are crushed), the MAH shall conduct and submit the results of a safety study conducted according to an agreed protocol. The clinical study report should be submitted by	June 2021

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

Dispersible tablets

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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.
Oral use.

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

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
Frimley Business Park
Camberley GU16 7SR
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

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

Dispersible tablets

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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.
Oral use.

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

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
Frimley Business Park
Camberley GU16 7SR
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

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 OF UNIT PACK

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

Dispersible tablets

28 dispersible tablets
84 dispersible tablets
252 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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.
Oral use.

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

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
Frimley Business Park
Camberley GU16 7SR
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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EXJADE 500 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (including blue box)

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

Dispersible tablets

Multipack: 294 (3 packs of 98) dispersible tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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.
Oral use.

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

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/010 294 (3 packs of 98) dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EXJADE 500 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (without blue box)

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

Dispersible tablets

98 dispersible tablets. Component of a multipack. Cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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.
Oral use.

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

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/010 294 (3 packs of 98) dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exjade 90 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/011	30 film-coated tablets
EU/1/06/356/012	90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 90 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 90 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack: 300 (10 packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/013 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 90 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 90 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/013 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 90 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Exjade 90 mg film-coated 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 OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exjade 180 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 180 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/014	30 film-coated tablets
EU/1/06/356/015	90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 180 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 180 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 180 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack: 300 (10 packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/016 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 180 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 180 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 180 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/016 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 180 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Exjade 180 mg film-coated 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 OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exjade 360 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 360 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/017	30 film-coated tablets
EU/1/06/356/018	90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 360 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 360 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 360 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack: 300 (10 packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/019 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 360 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exjade 360 mg film-coated tablets

deferasirox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 360 mg of deferasirox.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/356/019 300 (10 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exjade 360 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Exjade 360 mg film-coated 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 pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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). It traps and removes excess iron which is then excreted mainly in the stools.

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 (MDS)). 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.

2. What you need to know before you take EXJADE

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 any other iron chelator medicines.

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.
- 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). Your doctor may require you to undergo a kidney biopsy, if he/she suspects significant kidney damage. 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.

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

Other medicines and EXJADE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:
- other iron chelators, which must not be taken with EXJADE,
- antatacids (medicines used to treat heartburn) containing aluminium, which should not be taken at the same time of day as EXJADE,
- 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 (used for heart problems and migraines),
- 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
EXJADE can be used in children and adolescents receiving regular blood transfusions aged 2 years and over and in children and adolescents not receiving regular blood transfusions aged 10 years and over. As the patient grows the doctor will adjust the dose.

EXJADE is not recommended for children aged under 2 years.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

EXJADE is not recommended during pregnancy unless clearly necessary.

If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom), as EXJADE may reduce the effectiveness of oral and patch contraceptives.

Breast-feeding is not recommended during treatment with EXJADE.

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 for EXJADE dispersible tablets at the start of the treatment for patients receiving regular blood transfusions is 20 mg per kilogram body weight. A higher or lower starting dose may be recommended by your doctor based on your individual treatment needs.
- The usual daily dose for EXJADE dispersible tablets 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 for EXJADE dispersible tablets 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 children and adolescents not receiving regular blood transfusions.

Deferasirox also comes as “film-coated” tablets. If you are switching from the film-coated tablets to these dispersible tablets, you will need an adjustment of the dose.

When to take EXJADE

- Take EXJADE once a day, every day, at about the same time each day.
- Take the EXJADE dispersible 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 (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people).

- 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.

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

tell your doctor as soon as possible.

Other side effects
Very common (may affect more than 1 in 10 people)
- Disturbance in renal function tests.

Common (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.

Uncommon (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 after EXP. 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXJADE contains
The active substance is deferasirox.
- Each dispersible tablet of EXJADE 125 mg contains 125 mg deferasirox.
- Each dispersible tablet of EXJADE 250 mg contains 250 mg deferasirox.
- Each dispersible 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.
- 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.

EXJADE 125 mg, 250 mg and 500 mg dispersible tablets are available in unit packs containing 28, 84 or 252 dispersible tablets.
EXJADE 500 mg dispersible tablets are also available in multipacks containing 294 (3 packs of 98) dispersible tablets.
Not all pack sizes or strengths may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last revised in

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

Package leaflet: Information for the user

EXJADE 90 mg film-coated tablets
EXJADE 180 mg film-coated tablets
EXJADE 360 mg film-coated 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 pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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). It traps and removes excess iron which is then excreted mainly in the stools.

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 (MDS)). 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.

2. What you need to know before you take EXJADE

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 any other iron chelator medicines.

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
- 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). Your doctor may require you to undergo a kidney biopsy, if he/she suspects significant kidney damage. 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.

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

Other medicines and EXJADE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:
- other iron chelators, which must not be taken with EXJADE,
- antatacids (medicines used to treat heartburn) containing aluminium, which should not be taken at the same time of day as EXJADE,
- 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 (used for heart problems and migraines),
- 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
EXJADE can be used in children and adolescents receiving regular blood transfusions aged 2 years and over and in children and adolescents not receiving regular blood transfusions aged 10 years and over. As the patient grows the doctor will adjust the dose.

EXJADE is not recommended for children aged under 2 years.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

EXJADE is not recommended during pregnancy unless clearly necessary.

If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom), as EXJADE may reduce the effectiveness of oral and patch contraceptives.

Breast-feeding is not recommended during treatment with EXJADE.

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.

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 for EXJADE film-coated tablets at the start of the treatment for patients receiving regular blood transfusions is 14 mg per kilogram body weight. A higher or lower starting dose may be recommended by your doctor based on your individual treatment needs.
- The usual daily dose for EXJADE film-coated tablets at the start of the treatment for patients not receiving regular blood transfusions is 7 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 for EXJADE film-coated tablets is:
    - 28 mg per kilogram body weight for patients receiving regular blood transfusions,
    - 14 mg per kilogram body weight for adult patients not receiving regular blood transfusions,
    - 7 mg per kilogram body weight for children and adolescents not receiving regular blood transfusions.

Deferasirox also comes as “dispersible” tablets. If you are switching from the dispersible tablets to these film-coated tablets, you will need an adjustment of the dose.

When to take EXJADE

- Take EXJADE once a day, every day, at about the same time each day with some water.
- Take EXJADE film-coated tablets either on an empty stomach or with a light meal.

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

For patients who are unable to swallow whole tablets, EXJADE film-coated tablets may be crushed and taken by sprinkling the full dose onto soft food such as yogurt or apple sauce (pureed apple). The food should be immediately and completely consumed. Do not store it for future use.

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 (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people).

- 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.

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

tell your doctor as soon as possible.

Other side effects
Very common (may affect more than 1 in 10 people)

- Disturbance in renal function tests.

Common (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.

Uncommon (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 after EXP. The expiry date refers to the last day of that month.
- Do not use any pack that is damaged or shows signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXJADE contains
The active substance is deferasirox.
- Each film-coated tablet of EXJADE 90 mg contains 90 mg deferasirox.
- Each film-coated tablet of EXJADE 180 mg contains 180 mg deferasirox.
- Each film-coated tablet of EXJADE 360 mg contains 360 mg deferasirox.

The other ingredients are microcrystalline cellulose; crospovidone; povidone (K30); magnesium stearate; colloidal anhydrous silica and poloxamer 188. The tablet coating material contains: hypromellose; titanium dioxide (E171); macrogol (4000); talc; indigo carmine aluminium lake (E132).

What EXJADE looks like and contents of the pack
EXJADE is supplied as film-coated tablets. The film-coated tablets are ovaloid and biconvex.
- EXJADE 90 mg film-coated tablets are light blue and stamped “90” on one side and “NVR” on the other.
- EXJADE 180 mg film-coated tablets are medium blue and stamped “180” on one side and “NVR” on the other.
- EXJADE 360 mg film-coated tablets are dark blue and stamped “360” on one side and “NVR” on the other.

Each blister pack contains 30 or 90 film-coated tablets. The multipacks contain 300 (10 packs of 30) film-coated tablets.

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

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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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