EXJADE® (deferasirox)

250 mg, 500 mg dispersible tablets

180 mg, 360 mg film-coated tablets

LEAFLET

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Trade name

Exjade® 250 mg, 500 mg dispersible tablets

Exjade® 180 mg, 360 mg film-coated tablets

Description and composition

Pharmaceutical form(s)

Dispersible tablets.

Film-coated tablets.

Active substance(s)

Each dispersible tablet contains 250 mg / 500 mg deferasirox as active substance.
Each film-coated tablet contains 180 mg / 360 mg deferasirox as active substance.

Excipients

Exjade dispersible tablets

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

Exjade film-coated tablets

Microcrystalline cellulose; crospovidone; povidone (K30); magnesium stearate; colloidal silicon dioxide; poloxamer 188; coating material; hypromellose; titanium dioxide (E171); polyethylene glycol (4000); talc; FD&C blue #2/Indigo carminine aluminum lake (E132).

Indications

Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in β-thalassemia, sickle cell disease and other rare anemias in adult and pediatric patients (aged 6 years and over).

Exjade is also indicated in the management of chronic iron overload in pediatric patients aged 2 to 5 years who are unable to take deferoxamine therapy or in whom deferoxamine has proven ineffective.

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

Dosage and administration

Transfusional iron overload

Exjade dispersible tablets

Dosage

It is recommended that therapy with Exjade dispersible tablets be started after the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin > 1000 microgram/L). Doses

(in mg/kg) must be calculated and rounded to the nearest whole tablet size. Exjade dispersible tablets is available in two tablet strengths (250 mg and 500 mg).

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

For patients who are currently on chelation therapy with Exjade film-coated tablets and switching to Exjade dispersible tablets, the dose of Exjade dispersible tablets should be 40% higher than the dose of Exjade film-coated tablets, rounded to the nearest whole dispersible tablet.

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 receiving more than 14 mL/kg/month of packed red blood cells (approximately > 4 units/month for an adult), and for whom the objective is reduction of iron overload.

An initial daily dose of 10 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately < 2 units/month for an adult), and for whom the objective is maintenance of the body iron level.

For patients already well-managed on treatment with deferoxamine, a starting dose of Exjade dispersible tablets that is numerically half that of the deferoxamine dose could be considered as shown in Table 1 and 2 (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).

Dose adjusment

It is recommended that serum ferritin be monitored every month and that the dose of Exjade dispersible tablets 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 and to minimize the risk of overchelation (see section Warnings and precautions).

If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Exjade dispersible tablets may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section Warnings and Precautions).

EXJADE film-coated tablets

Dosage

It is recommended that therapy with Exjade film-coated tablets be started after the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 microgram/L). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

Exjade film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade dispersible tablet formulation (see section Clinical Pharmacology). For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Exjade film-coated tablet, the dose of Exjade film-coated tablet should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet, as shown in table 3.

Starting dose

The recommended initial daily dose of Exjade film-coated tablet is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg may be considered for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately >4 units/month for an adult), and for whom the objective is reduction of iron overload.

An initial daily dose of 7 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult), and for whom the objective is maintenance of the body iron level. For patients already well-managed on treatment with deferoxamine, a starting dose of Exjade film-coated tablet that is numerically one third 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 tablet).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of Exjade film-coated tablet is 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 2500 microgram/L and not showing a

decreasing trend over time), doses of up to 28 mg/kg may be considered. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with dose 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 microgram/L and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range and to minimize the risk of overchelation (see section Warnings and precautions). If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Exjade film-coated tablet may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section Warnings and precautions).

The corresponding recommended doses for both formulations are shown in Table 1.

Table 1 Transfusional iron overload: Recommended doses

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

* Packed Red Blood Cells
** Dose conversion explained in more detail in the Table 3

Non-transfusion-dependent thalassemia (NTDT) syndromes

Exjade dispersible tablets

Dosage

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) **and** serum ferritin consistently >800 microgram/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation.

For patients who are currently on chelation therapy with Exjade film-coated tablet and switching to Exjade dispersible tablet, the dose of Exjade dispersible tablet should be 40% higher than the dose of Exjade film-coated tablet, rounded to the nearest whole dispersible tablet.

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 to assess the patient's response to therapy and to minimize the risk of overchelation (see Warnings and precautions). 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 serum ferritin is consistently >2,000 microgram/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 thalassemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 microgram/L, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 microgram/L.

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

Exjade film-coated tablets

Dosage

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 microgram/L). In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation.

Exjade film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade dispersible tablet formulation (see section Clinical Pharmacology). For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Exjade film-coated tablet, the dose of Exjade film-coated tablet should be 30% lower than the dose of Exjade dispersible tablet, rounded to the nearest whole tablet.

Starting dose

The recommended initial daily dose of Exjade film-coated tablet is 7 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see Warnings and precautions). Every 3 to 6 months of treatment, consider a dose increase in increments of 3.5 to 7 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 microgram/L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.

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

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

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

The corresponding recommended doses for both formulations are shown in Table 2

Table 2 NTDT: Recommended doses

	Exjade Dispersible tablets	**Exjade Film-coated tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	10 mg/kg/day	7 mg/kg/day	≥5 mg Fe/g dw	or	>800 µg/l
Adjustment steps (every 3-6 months)	Increase 5-10 mg/kg/day	Increase 3.5 - 7 mg/kg/day	≥7 mg Fe/g dw	or	>2,000 µg/l
	Decrease 5-10 mg/kg/day	Decrease 3.5 - 7 mg/kg/day	<7 mg Fe/g dw	or	≤2,000 µg/l
Maximum dose	20 mg/kg/day	14 mg/kg/day			
	10 mg/kg/day	7 mg/kg/day	Not assessed	and	≤2,000 µg/l
Dose Interruption			<3 mg Fe/g dw	or	<300 µg/l
Reinitiation			if clinical evidence of chronic iron overload		

*LIC is the preferred method of determining iron overload

Transfusional iron overload and non-transfusion-dependent thalassemia syndromes

Information on dose conversion between DT and FCT, as well as deferoxamine is shown in Table 3 below.

Table 3 Dose conversion

Deferoxamine dose**	Daily dose of Exjade Dispersible tablets	Daily dose for Exjade Film-coated tablets/granules
10 mg/kg	5 mg/kg	3.5 mg/kg
20 mg/kg	10 mg/kg	7 mg/kg
30 mg/kg	15 mg/kg	10.5 mg/kg
40 mg/kg	20 mg/kg	14 mg/kg
50 mg/kg	25 mg/kg	17.5 mg/kg
60 mg/kg	30 mg/kg	21 mg/kg
Not applicable*	35 mg/kg	24.5 mg/kg
Not applicable*	40 mg/kg	28 mg/kg

* Not recommended in deferoxamine label

****For patients already well-managed on treatment with deferoxamine**

Special populations:

Patients with renal impairment

Exjade dispersible tablets

Exjade dispersible tablet treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 10 mg/kg (see section Warnings and Precautions).

Exjade film-coated tablets

Exjade film-coated tablet treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. The initial dosing recommendations for patients with renal impairment are the same as described above. Serum creatinine should be monitored monthly in all patients and if necessary daily doses can be reduced by 7 mg/kg (see section Warnings and precautions).

Patients with hepatic impairment

Deferasirox has been studied in a clinical trial in subjects with hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by 50%. Exjade should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section Warnings and precautions and section Clinical pharmacology). Hepatic function in all patients should be

monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see section Warnings and Precautions).

Pediatric patients
The dosing recommendations for pediatric patients are the same as for adult patients. It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see section Warnings and Precautions). Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

Elderly patients

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

Method of administration

Exjade dispersible tablets

Exjade dispersible tablets must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be resuspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

Exjade film-coated tablets

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

Exjade 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 section Clinical Pharmacology).

Contraindications

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

High risk myelodysplastic syndrome (MDS) patients and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

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

Warnings and Precautions

The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy (see section Dosage and Administration).
Caution should be used in elderly patients due to a higher frequency of adverse reactions.

Renal Impairment

Non-progressive rises in serum creatinine have been noted in patients treated with deferasirox, usually within the normal range. Cases of acute renal failure have been reported following the post-marketing use of deferasirox (see section Adverse Drug Reactions). Although causal relationship with EXJADE could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy and monitored monthly thereafter.

Patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function may be more at risk of complications. Therefore, serum creatinine and/or creatinine clearance should be monitored weekly in the first month after initiation or modification of therapy (including switching formulation), and monthly thereafter. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

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

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

Tests for proteinuria should be performed monthly.

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

For adult patients, the daily dose of Exjade dispersible tablets may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section Dosage and Administration). For pediatric patients, the dose may be reduced by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

For adult patients, the daily dose of Exjade film-coated tablets may be reduced by 7 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section 4 Dosage and administration). For pediatric patients, the dose may be reduced by 7 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, Exjade dispersible tablets/Exjade film-coated tablets should be interrupted. Therapy with Exjade dispersible tablets/Exjade film-coated tablets may be reinitiated depending on the individual clinical circumstances.

Hepatic impairment

Exjade dispersible tablets/Exjade film-coated tablets is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see section Dosage and administration and Clinical pharmacology).

Deferasirox treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox was not influenced by such transaminase levels. Deferasirox is principally eliminated by glucuronidation and is minimally (about 8%) metabolized by oxidative cytochrome P450 enzymes (see section Clinical Pharmacology).

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials. There have been postmarketing reports of hepatic failure in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients (see section Adverse Drug Reactions). It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, Exjade dispersible tablets/Exjade film-coated tablets should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of Exjade dispersible tablets/Exjade film-coated tablets treatment at a lower dose followed by gradual dose escalation may be considered.

Blood Disorders

There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had preexisting haematologic disorders that are frequently associated with bone marrow failure (see section Adverse Drug Reactions). The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such haematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with Exjade dispersible tablets/Exjade film-coated tablets should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with Exjade dispersible tablets/Exjade film-coated tablets may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal Disorders

Gastrointestinal irritation may occur during Exjade dispersible tablets/Exjade film-coated tablets treatment. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. There have been rare reports of fatal GI haemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients (see section Adverse Drug Reactions). Physicians and patients should remain alert for signs and symptoms of GI ulceration and haemorrhage during Exjade dispersible tablets/Exjade film-coated tablets therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

Caution should be exercised in patients who are taking Exjade dispersible tablets/Exjade film-coated tablets in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see section Interactions), and in patients with platelet counts $<50 \times 10^9$/L.

Hypersensitivity reactions

Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section Adverse Drug Reactions). If reactions are severe, Exjade dispersible tablets/Exjade film-coated tablets should be discontinued and appropriate medical intervention instituted. Exjade dispersible tablets/Exjade film-coated tablets should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

Skin disorders

Severe cutaneous adverse reactions (SCRAs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life threatening or fatal have been reported. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If any SCAR is suspected Exjade dispersible tablets/Exjade film-coated tablets should be discontinued immediately and should not be reintroduced.

Rare cases of erythema multiforme have been reported during Exjade dispersible tablets/Exjade film-coated tablets treatment.

Skin rashes may appear during Exjade dispersible tablets/Exjade film-coated tablets treatment. For rashes of mild to moderate severity, Exjade dispersible tablets/Exjade film-coated tablets may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Exjade dispersible tablets/Exjade film-coated tablets may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation.

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment (see section Adverse Drug Reactions). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Exjade dispersible tablets/Exjade film-coated tablets treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.

Other considerations

As with other iron chelator treatment, the risk of toxicity of Exjade dispersible tablets/Exjade film-coated tablets may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. Closer monitoring of serum ferritin levels, as well as renal and hepatic function is recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. Dose reduction may be considered to avoid overchelation (see section Dosage and administration).

Deferasirox has not been associated with growth retardation in children followed for up to 5 years in clinical trials with the dispersible tablet formulation. However, as a general precautionary measure, body

weight and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

The dispersible tablets contain lactose (1.1 mg lactose for each mg of deferasirox). This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

Patients should be cautioned not to take aluminium containing antacids and Exjade dispersible tablets/Exjade film-coated tablets simultaneously.

Driving and using machines

No studies on the effects of Exjade dispersible tablets/Exjade film-coated tablets on the ability to drive and use machines have been performed. Patients experiencing the uncommon adverse effect of dizziness should exercise caution when driving or operating machinery.

Adverse drug reactions

Summary of the safety profile

In clinical trials in patients with transfusional iron overload, the most frequent reactions reported during chronic treatment with the deferasirox dispersible tablet formulation in adult and pediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea, or abdominal pain and skin rash in about 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see section Warnings and Precautions).

In clinical trials of the deferasirox dispersible tablet formulation in patients with transfusional iron overload, elevations of liver transaminases were reported in about 2% of patients. These were not dependent on dose and most of these patients had elevated levels prior to receiving deferasirox. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). There have been postmarketing reports of hepatic failure in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

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

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 Warnings and precautions).

The following adverse drug reactions, listed in Table 4, have been reported in clinical studies following treatment with deferasirox dispersible tablet. Adverse reactions are ranked below using the following

convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated summary of Adverse drug reactions from clinical trials

Table 4 Adverse drug reactions reported in clinical studies

Psychiatric disorders	
Uncommon:	anxiety, sleep disorder
Nervous system disorders	
Common:	headache
Uncommon:	dizziness
Eye disorders	
Uncommon:	cataract, maculopathy
Rare:	optic neuritis
Ear and labyrinth disorders	
Uncommon:	deafness
Respiratory, thoracic and mediastinal disorders	
Uncommon:	laryngeal pain
Gastrointestinal disorders	
Common:	diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis
Rare:	oesophagitis
Hepatobiliary disorders	
Common:	transaminases increased
Uncommon:	hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritus
Uncommon:	pigmentation disorder
Rare:	erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	
Very common:	blood creatinine increased
Common:	proteinuria
Uncommon	renal tubular disorder (Fanconi's syndrome)
General disorders and administration site conditions	
Uncommon:	pyrexia, oedema, fatigue

In a study to assess the safety of deferasirox film-coated and dispersible tablets, 173 adult and pediatric patients with transfusion-dependent thalassemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed.

Listing of Adverse drug reactions from post-marketing spontaneous reports

Other adverse events that were reported in clinical studies are: cough, nasopharingitis, influenza, respiratory tract infections, bronchitis, pharingitis, athralgia, acute tonsillitis, ear infection and urticaria.

Spontaneously reported adverse reactions, presented in Table 5, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 5 Adverse drug reactions derived from spontaneous reports (frequency not known)

Renal and urinary disorders renal tubular necrosis, acute renal failure (mostly serum creatinine increases ≥ 2x upper limit of normal, and usually reversible after treatment interruption), tubulointerstitial nephritis
Gastrointestinal disorders gastrointestinal perforation
Hepatobiliary disorders hepatic failure
Skin and subcutaneous tissue disorders Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
Immune system disorders hypersensitivity reactions (including anaphylactic reaction and angioedema)

Description of selected adverse drug reactions

Cytopenias

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia, thrombocytopenia and aggravated anemia in patients treated with deferasirox. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure (see section Warnings and precautions for use). The relationship of these episodes to treatment with deferasirox is uncertain.

Pancreatitis

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

Pediatric population

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

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

Interactions

Agents that may decrease Exjade dispersible tablet/Exjade film coated tablet systemic exposure

In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of Exjade dispersible tablet/Exjade film-coated tablet with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade dispersible tablet/Exjade film-coated tablet efficacy. If Exjade dispersible tablet/Exjade film-coated tablet and a potent UGT inducer are used concomitantly, increases in the dose of Exjade dispersible tablet/Exjade film-coated tablet should be considered based on clinical response to therapy.

Interaction with food

Exjade dispersible tablets

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

Exjade film-coated tablets

The C_{max} of deferasirox film-coated tablets was moderately increased (by 29%) when taken with a high-fat meal. Exjade film-coated tablet may be taken either on an empty stomach or with a light meal, preferably at the same time each day (see Section Clinical Pharmacology).

Interaction with midazolam and other agents metabolized by CYP3A4

In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablet and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% to 26%). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents).

Interaction with repaglinide and other agents metabolized by CYP2C8

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

Interaction with theophylline and other agents metabolized by CYP1A2

In a healthy volunteer study, the concomitant administration of deferasirox (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates may be possible.

Interaction with busulfan

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

Other Information

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

The concomitant administration of deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences.

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

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

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

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

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

As a precaution, it is recommended that Exjade dispersible tablet/Exjade film-coated tablet not be used during pregnancy unless clearly necessary.

Data

Animal data

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.

Lactation

Risk summary

It is not known if deferasirox is transferred into human milk.

In animal studies, deferasirox was found to be rapidly and extensively transferred into maternal milk. No effects on the offspring were noted at maternally non-toxic doses of deferasirox. Breast-feeding while taking Exjade dispersible tablet/Exjade film-coated tablet is not recommended.

Females and males of reproductive potential

Contraception

Caution should be exercised when deferasirox is combined with hormonal contraceptive agents that are metabolized through CYP3A4 due to a possible decrease in efficacy of contraceptive agents (see section Interactions).

Infertility

Deferasirox did not affect fertility or reproduction in rat studies even at toxic doses (see section Non-clinical safety data).

Overdosage

Single doses up to 40 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 28 mg/kg Exjade film-coated tablet) in normal subjects have been well tolerated.

Early signs of acute overdose are digestive effects such as abdominal pain, diarrhea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine

increased with recovery after treatment discontinuation. An errenously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.

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

Clinical pharmacology

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

Mechanism of action

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

Pharmacodynamics (PD)

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

Deferasirox has been investigated in adult and pediatric patients (aged 2 years and older) with chronic iron overload due to blood transfusions. The underlying conditions requiring transfusion included beta-thalassemia, sickle cell disease, and other congenital and acquired anemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anaemia and other very rare anemias).

Daily treatment with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and pediatric patients with beta-thalassemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight) on average, respectively, and serum ferritin was reduced by about -36 and -926 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 anemias. Daily doses of 10 mg/kg (dispersible tablet formulation) for one year could maintain liver iron and serum ferritin levels, and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions (see Section Dosage and Administration). Serum ferritin assessed by monthly monitoring reflected changes in liver iron concentration indicating that trends in serum ferritin can be used to monitor response to therapy.

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

Pharmacokinetics (PK)

Exjade film-coated Tablets

Exjade film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the EXJADE dispersible tablet formulation. After strength-adjustment, the film-coated tablet formulation (360 mg strength) was equivalent to Exjade 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 has revealed no evidence of clinically relevant effects of such an increase.

Absorption

Exjade dispersible tablets

Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) was about 70% compared to an intravenous dose. Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approx. 13 to 25%) elevated when taken 30 minutes before meals with normal or high fat content. The total exposure (AUC) to deferasirox when taken after dispersion of tablets in orange juice or apple juice was equivalent to the exposure after dispersion in water (relative AUC ratios of 103% and 90%, respectively).

Exjade film-coated Tablets

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

Biotransformation

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling)

is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No inhibition of deferasirox metabolism by hydroxyurea was observed in vitro. Deferasirox undergoes enterohepatic recycling. In a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

Elimination

Deferasirox and its metabolites are primarily excreted in the faeces (84% of the dose). Renal excretion of deferasirox and its metabolites is minimal (8% of the dose). The mean elimination half-life ($T_{1/2}$) ranged from 8 to 16 hours.

Linearity / non-linearity

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

Special Populations

Pediatric patients

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

Gender

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

Elderly patients

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

Renal or hepatic impairment

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

Clinical studies

Clinical efficacy studies were conducted with deferasirox dispersible tablet. An open-label, randomized, Phase III, active comparator control study to compare deferasirox dispersible tablets and Desferal (deferoxamine) was conducted in patients with beta-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral deferasirox at starting doses of 5, 10, 20 or 30 mg/kg once daily or subcutaneous deferoxamine at starting doses of 20 to 60 mg/kg

for at least 5 days per week based on liver iron concentration (LIC) at baseline (2 to 3, >3 to 7, >7 to 14 and >14 mg Fe/g dry weight (dw)). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dw were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

LIC was assessed at baseline and after 12 months of therapy by liver biopsy or non-invasively by biomagnetic susceptometry. Success rate, the primary efficacy endpoint, was defined as a reduction in LIC of ≥3 mg Fe/g dw for baseline values ≥10 mg Fe/g dw, reduction of baseline values between 7 and <10 to <7 mg Fe/g dw, or maintenance or reduction for baseline values <7 mg Fe/g dw. Deferasirox was to be declared non-inferior to deferoxamine if the lower limit of the 95% confidence interval (two-sided) of the difference in success rates was above -15%.

In total, 586 patients were randomized. Demographics were well balanced. Fifty-one percent of the patients were <16 years of age. The overall success rates were 52.9% for deferasirox and 66.4% for deferoxamine with a difference of -13.5 in success rates and a 95% CI of [-21.6, -5.4]. Non-inferiority to deferoxamine was not achieved because the lower limit of the CI was below -15%. This is attributed to the imbalance of the protocol-specified dose to the actual dose in the two lowest dose cohorts of the deferoxamine arm (Table 6). However, non-inferiority was demonstrated in a group of patients with baseline LIC levels ≥7 mg Fe/g dw who were allocated to the higher dose groups (deferasirox doses of 20 or 30 mg/kg and deferoxamine doses of ≥35 mg/kg). The success rates with deferasirox and deferoxamine were 58.6% and 58.9%, respectively, and the lower limit of the 95% CI (-10.2%) was above the non-inferiority threshold of -15%.

In patients with LIC ≥7 mg Fe/g dw who were treated with deferasirox 20 to 30 mg/kg per day, a statistically significant reduction in LIC from baseline was observed (-5.3 ± 8.0 mg Fe/g dw, p <0.001, t-test) which was not statistically significantly different from deferoxamine (-4.3 ± 5.8 mg Fe/g dw, p = 0.367). Dose dependent effects in serum ferritin and in the ratio of iron excretion/iron intake from deferasirox doses of 5 to 30 mg/kg were also observed (Table 6).

Table 6 Ratio of iron excretion/iron intake and change in serum ferritin levels from baseline to 1 year of treatment in the primary efficacy study.

Protocol recommended dose (mg/kg/day)		Mean actual prescribed dose (mg/kg/day)		Ratio of iron excretion / iron intake		Serum ferritin levels (microgram/L) Mean change from baseline ± SD	
Deferasirox	Defer-oxamine	Deferasirox	Defer-oxamine	Deferasirox Mean ± SD (n)	Defer-oxamine Mean ± SD (n)	Deferasirox Mean ± SD (n)	Defer-oxamine Mean ± SD (n)
5	20-30	6.2 ± 1.6	33.9 ± 9.9	0.58 ± 0.328 (15)	0.95 ± 0.101 (13)	+1189 ± 700 (15)	+211 ± 459 (13)
10	25-35	10.2 ± 1.2	36.7 ± 9.2	0.67 ± 0.365 (68)	0.98 ± 0.217 (75)	+833 ± 817 (73)	+32 ± 585 (77)
20	35-50	19.4 ± 1.7	42.4 ± 6.6	1.02 ± 0.398 (77)	1.13 ± 0.241 (87)	-36 ± 721 (80)	-364 ± 614 (89)
30	≥50	28.2 ± 3.5	51.6 ± 5.8	1.67 ± 0.716 (108)	1.44 ± 0.596 (98)	-926 ± 1416 (115)	-1003 ± 1428 (101)

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

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other, n=22). Nineteen percent of patients were <16 years of age and 16% were ≥65. Thirty-seven patients had not received prior chelation therapy. In the total population, the success rate (50.5%) was not statistically significantly higher than 50%. This was attributed to the fact that the doses of 5 and 10 mg/kg were insufficient for the ongoing rate of iron intake from blood transfusions. However, in patients with LIC ≥7 mg Fe/g dw for whom both baseline and end of study LIC was available and who received deferasirox 20 to 30 mg/kg per day, the success rate was 58.5% [p=0.022 (50.3, 66.6)] and there was a statistically significant reduction in the absolute LIC from baseline to end of study (-5.5 ± 7.4 mg Fe/g dw, p <0.001, t-test). There was also a dose dependent effect on serum ferritin and the ratio of iron excretion to iron intake from doses of 5 to 30 mg/kg per day.

A third study was conducted in patients with sickle cell disease and transfusional hemosiderosis. This study was an open-label, randomized, Phase II study of the safety and efficacy of deferasirox dispersible tablet relative to deferoxamine given for 1 year. Patients were randomized to deferasirox at doses of 5, 10, 20, or 30 mg/kg per day or subcutaneous deferoxamine at doses of 20 to 60 mg/kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with deferasirox and 63 with deferoxamine. Forty-four percent of patients were <16 years of age and 91% were Black. At the end of the study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least one post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

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

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

A cardiac sub-study was conducted as part of a Phase IV study with deferasirox dispersible tablet. The cardiac sub-study was a one year, prospective, open-label, single-arm study which included two cohorts of severely iron overloaded beta-thalassemia patients with LVEF values ≥56%: 114 patients with baseline T2* values >5 to <20 ms indicating myocardial siderosis (treatment cohort) and 78 patients with myocardial T2* ≥20 ms indicating no clinically significant cardiac iron deposition (prevention cohort). In the treatment cohort, the deferasirox starting dose was 30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. In the prevention cohort, the deferasirox starting dose was 20-30 mg/kg/day, with escalation to a maximum of 40 mg/kg/day. The primary endpoint of the cardiac sub-study was the change in T2* at one year. In the treatment cohort, T2* (geometric mean ± coefficient of variation) significantly increased from a baseline value of 11.2 ms ± 40.5% to 12.9 ms ± 49.5%, representing a significant improvement of 16% (p <0.0001). In the treatment cohort, improvement in T2* was observed in 69.5% of patients and stabilization of T2* in 14.3% of patients. LVEF remained stable and within the normal range: 67.4 ± 5.7% to 67.1 ± 6.0%. In the prevention cohort, myocardial T2* remained within

the normal range and was unchanged from a baseline value of 32.0 ms ± 25.6% to 32.5 ms ± 25.1% (+2%; p = 0.565) indicating that daily treatment with deferasirox can prevent cardiac iron loading in beta-thalassemia patients with a history of high transfusion exposure, and regular, ongoing transfusions.

Patients in the treatment cohort of the 1-year core study had the option to participate in two 1-year extensions. Over a three-year treatment duration period, there was a statistically significant (p<0.0001), progressive and clinically relevant increase in the geometric mean of cardiac T2* from baseline overall, in the severe cardiac iron overload sub-group, which is associated with a high risk of cardiac failure (T2* >5 to <10 ms), and in the mild to moderate cardiac iron overload sub-group (T2* 10 to <20 ms) (Table-7). Using the geometric mean ratio, the T2* increase was 43% above baseline in all patients, 37% increase from baseline in the T2* >5 to <10 ms sub-group, and 46% increase from baseline in the T2* 10 to <20 ms sub-group. Continuous treatment with deferasirox dispersible tablet for up to 3 years at doses >30 mg/kg/day effectively reduced cardiac iron in thalassemia major patients with myocardial siderosis as shown by the number of patients who normalized their T2* or improved to a category associated with a lower risk of cardiac failure (Table-8).

Table-7 Geometric mean of T2* (ms) at baseline, and at the end of year 1, 2, and 3

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

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

Table-8 Transition table of cardiac T2* from core baseline to end of E2 (year 3)

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

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with deferasirox dispersible tablet was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of matching placebo (56 patients). The study enrolled 145 adult and 21 pediatric 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 tablet 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 (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 (starting dose 10 mg/kg/day) and increased by 115 µg/l in patients treated with placebo ($p<0.001$).

In a study to assess the safety of deferasirox film-coated and dispersible tablets, 173 adult and pediatric patients with transfusion-dependent thalassemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed. Increased adherence to treatment, higher patient satisfaction and better palatability were reported in the film-coated tablet arm.

Non-clinical safety data

Preclinical data reveal no special hazard for patients with iron overload, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. The main findings were kidney toxicity and lens opacity (cataracts). Similar findings were observed in neonatal and juvenile animals. The kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron.

See section Pregnancy, lactation, females and males of reproductive potential.

Pharmaceutical information

Incompatibilities

Exjade dispersible tablets

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

Exjade film-coated tablets

Not applicable.

Special precautions for storage

Do not store above 30°C.

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

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

Shelf-life

See outer package.

Instructions for use and handling

No special requirements.

Package

Exjade® Dispersible tablet 250 mg: Box, 4 blisters @ 7 tablets, Reg. No.
Exjade® Dispersible tablet 500 mg: Box, 4 blisters @ 7 tablets, Reg. No.
Exjade® Film-coated tablet 180 mg: Box, 3 blisters @ 10 film-coated tablets, Reg. No. DKI2257000217B1
Exjade® Film-coated tablet 360 mg: Box, 3 blisters @ 10 film-coated tablets, Reg. No. DKI2257000217C1

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician

Manufacturer's Information

Exjade Film-coated Tablet

Manufactured by Sandoz S.R.L., Targu Mures, Romania for Novartis Pharma AG, Basel, Switzerland Imported by PT Novartis Indonesia, Jakarta, Indonesia

Exjade Dispersible Tablet

Manufactured by Sandoz S.R.L., Targu Mures, Romania for Novartis Pharma AG, Basel, Switzerland Imported by PT Novartis Indonesia, Jakarta, Indonesia

Leaflet based on CDS 24-Jul-2019 *and change of manufacturing site to Targu Mures*

NOVARTIS

EXJADE® (deferasirox)

Tablet dispersibel 250 mg, dan 500 mg

Tablet salut selaput 180 mg dan 360 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM: 21/06/2024

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Bacalah brosur ini dengan saksama sebelum Anda mengonsumsi Exjade®

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter atau apoteker Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Jika Anda mengalami efek samping yang berat, atau jika Anda mengalami efek samping yang tidak tertera pada brosur ini, mohon informasikan kepada dokter ataupun apoteker Anda.

1 Apakah EXJADE® dan apa kegunaannya

Apakah EXJADE® itu

EXJADE tablet dispersibel

EXJADE 250 mg dan 500 mg tablet dispersibel mengandung zat aktif yang disebut deferasirox. Obat ini merupakan kelasi (*chelator)* besi yang berfungsi mengeluarkan kelebihan zat besi dari dalam tubuh (kondisi kelebihan zat besi kadang disebut sebagai *iron overload*).

EXJADE tablet salut selaput

EXJADE 180 mg dan 360 mg tablet salut selaput mengandung zat aktif yang disebut deferasirox. Obat ini merupakan kelasi (*chelator)* besi yang berfungsi mengeluarkan kelebihan zat besi dari dalam tubuh (kondisi kelebihan zat besi kadang disebut sebagai *iron overload*).

Apa kegunaan EXJADE®

- Kelebihan zat besi *transfusional* (kelebihan zat besi pada pasien yang menerima transfusi darah rutin)

  EXJADE digunakan untuk mengobati kelebihan zat besi yang disebabkan oleh transfusi darah berulang pada pasien penderita anemia jenis tertentu misalnya talasemia, penyakit sel sabit (*sickle cell disease*). EXJADE dapat digunakan untuk mengobati pasien dewasa dan anak-anak (usia 6 tahun keatas). EXJADE juga dapat digunakan untuk mengobati kelebihan zat besi pada pasien anak-anak usia 2 – 5 tahun yang tidak dapat menerima pengobatan dengan deferoxamine atau ketika pengobatan dengan deferoxamine tidak efektif.

  Transfusi darah berulang dapat menyebabkan penumpukan kadar zat besi di dalam tubuh. Hal ini dikarenakan sel darah mengandung zat besi dan tubuh Anda memiliki keterbatasan dalam cara alami untuk membuang kelebihan zat besi yang didapat dari transfusi darah.
- Sindrom talasemia yang tidak tergantung transfusi atau *Non-Transfusion Dependent Thalassemia* (yang merupakan kelebihan zat besi pada pasien penderita talasemia yang bukan disebabkan oleh transfusi darah rutin)

  EXJADE dapat digunakan untuk mengobati pasien dengan kelebihan zat besi sehubung dengan sindrom talasemia yang tidak tergantung transfusi. Untuk kasus ini, EXJADE dapat

digunakan untuk mengobati pasien dewasa, remaja dan anak-anak usia 10 tahun ke atas. Pada pasien dengan sindrom talasemia yang tidak tergantung transfusi, kelebihan zat besi dapat berkembang dari waktu ke waktu terutama karena peningkatan penyerapan zat besi dari makanan akibat rendahnya jumlah sel darah. Pada pasien talasemia yang tidak mendapatkan transfusi darah secara teratur, peningkatan kadar zat besi biasanya baru terlihat pada pasien usia 10 tahun ke atas.

Seiring dengan waktu, kelebihan zat besi dapat merusak organ-organ penting seperti hati dan jantung.

Obat-obatan yang disebut dengan kelasi (*chelator*) besi digunakan untuk mengeluarkan kelebihan zat besi dan mengurangi resiko kerusakan organ karena kelebihan zat besi.

Bagaimana cara kerja EXJADE

EXJADE bekerja dengan cara mengikat zat besi berlebih dalam tubuh dan mengeluarkannya melalui *feses*/kotoran.

Jika Anda memiliki pertanyaan lebih lanjut terkait cara kerja EXJADE atau kenapa Anda diresepkan obat ini, tanyakan kepada dokter, apoteker atau tenaga kesehatan.

2 Sebelum mengonsumsi EXJADE

Ikuti semua petunjuk yang diberikan dokter Anda dengan saksama meskipun informasi tersebut dapat berbeda dengan informasi yang tercantum pada brosur ini.

Jangan mengonsumsi EXJADE

- **Jika anda mengalami alergi** (hipersensitivitas) terhadap deferasirox atau terhadap kandungan zat lain yang terdapat pada EXJADE. Jika Anda mengira Anda mengalami alergi, berkonsultasilah dengan dokter Anda.
- Jika Anda memiliki masalah pada ginjal yang serius.
- Jika Anda menderita sindrom *myelodysplastic* stadium lanjut atau kanker stadium lanjut.

Jika ada kondisi diatas yang berlaku untuk Anda, **jangan mengonsumsi EXJADE dan beritahukan kepada dokter Anda.**

Peringatan dan Perhatian

Jika ada kondisi di bawah ini yang berlaku untuk Anda, beritahukan kepada dokter, apoteker atau tenaga kesehatan Anda sebelum mengonsumsi EXJADE:

- Jika Anda memiliki masalah pada ginjal.
- Jika Anda sedang atau baru saja mengonsumsi obat penghilang rasa sakit, obat anti-inflamasi atau obat golongan bifosfonat.
- Jika Anda sedang atau baru saja mengonsumsi obat antikoagulan (obat anti penggumpalan darah).
- Jika hasil tes darah Anda menunjukan kadar trombosit atau sel darah putih yang rendah.

Jika ada kondisi di bawah ini selama mengonsumsi EXJADE yang berlaku untuk Anda, beritahukan kepada dokter, apoteker atau tenaga kesehatan Anda:

- Jika Anda mengalami muntah darah dan/atau *feses* yang berwarna kehitaman.
- Jika Anda sering mengalami sakit perut terutama setelah mengonsumsi EXJADE.
- Jika Anda mengalami penurunan volume urin (hal ini dapat menandakan adanya masalah pada ginjal).
- Jika Anda mengalami ruam parah, atau kesulitan bernafas dan pusing atau pembengkakan terutama pada wajah dan tenggorokan (hal ini dapat menandakan gejala dari reaksi alergi berat).
- Jika Anda mengalami kombinasi dari gejala berikut ini: ruam, kulit kemerahan, kulit pecah pada daerah sekitar bibir, mata atau mulut, pengelupasan kulit, demam tinggi, gejala flu dan pembesaran kelenjar getah bening (hal ini dapat menandakan reaksi kulit berat).
- Jika Anda mengalami rasa mengantuk berlebih, nyeri pada perut bagian kanan atas, timbulnya warna kekuningan pada kulit atau mata dan urin berwarna gelap (hal ini dapat menandakan masalah pada hati).
- Jika Anda mengalami masalah pada penglihatan atau pendengaran.

Cara memonitor pengobatan dengan EXJADE

Anda mungkin akan mendapatkan beberapa tes rutin (darah, urin atau *Magnetic Resonance Imaging (MRI)*) sebelum dan selama pengobatan dengan EXJADE. Tes ini ditujukan untuk memonitor kadar zat besi dalam tubuh Anda untuk melihat efektivitas EXJADE (kadar ferritin, kandungan zat besi dalam hati dan/atau jantung). Tes ini juga bertujuan memonitor fungsi ginjal Anda (kadar kreatinin dalam darah, jumlah protein dalam urin) dan fungsi hati Anda (kadar transaminase, bilirubin dan alkalin fosfatase dalam darah). Hasil tes ini akan digunakan oleh dokter Anda untuk mempertimbangkan pemilihan dosis EXJADE yang paling tepat untuk Anda dan kapan Anda dapat menghentikan pengobatan dengan EXJADE.

Sebagai bagian dari monitoring dan pencegahan, penglihatan dan pendengaran Anda juga akan di tes sekali dalam setahun.

Jika Anda memiliki pertanyaan lebih lanjut terkait cara kerja EXJADE atau mengapa Anda diresepkan obat ini, Anda dapat bertanya kepada dokter atau apoteker Anda.

Pasien Usia Lanjut (usia 65 tahun keatas)

EXJADE dapat dikonsumsi oleh pasien berusia 65 tahun keatas dengan dosis yang sama dengan dosis untuk pasien dewasa. Pasien usia lanjut dapat mengalami lebih banyak efek samping dibandingkan pasien yang lebih muda. Mereka harus mendapatkan pengawasan ketat dari dokter untuk kemungkinan efek samping yang memerlukan penyesuaian dosis.

Anak-anak dan remaja (usia 2 sampai 17 tahun)

EXJADE dapat dikonsumsi oleh pasien remaja dan anak-anak usia 2 tahun keatas. Seiring dengan masa pertumbuhan pasien, dokter dapat melakukan penyesuaian dosis.

Mengonsumsi obat lain

Antasida (obat yang digunakan untuk mengatasi nyeri perut) yang mengandung aluminium tidak boleh diminum pada waktu yang sama dengan EXJADE.

Mohon beritahukan dokter atau apoteker Anda jika Anda sedang atau baru saja mengonsumsi obat-obatan lain, termasuk obat-obatan yang bisa didapat tanpa resep dokter.

Khususnya jika Anda mengonsumsi obat-obatan di bawah ini:

- Midazolam (digunakan untuk meredakan kecemasan dan/atau gangguan tidur)
- Siklosporin (digunakan pada pasien yang mengalami transplantasi organ untuk mencegah terjadinya penolakan organ transplan, atau untuk kondisi lain contohnya: *rheumatoid arthritis* atau *dermatitis atopic*.
- Simvastatin (obat penurun kolesterol)
- Kontrasepsi hormonal (obat pengontrol kehamilan)
- Beberapa obat penghilang rasa sakit atau anti-inflamasi (contohnya: aspirin, ibuprofen, kortikosteroid).
- Bifosfonat oral (digunakan untuk mengobati osteoporosis)
- Obat antikoagulan (digunakan untuk mencegah atau mengobati penggumpalan darah)
- Repaglinide (untuk pengobatan diabetes)
- Rifampicin (untuk pengobatan tuberkulosis)
- Fenitoin, fenobarbital (untuk pengobatan epilepsi)
- Ritonavir (untuk pengobatan infeksi HIV)
- Paclitaxel (untuk pengobatan kanker)
- Teofilin (untuk pengobatan penyakit pernafasan seperti asma)
- Busulfan (digunakan untuk pengobatan sebelum transplantasi sumsum tulang)

Dokter Anda mungkin perlu menguji kadar obat-obat tersebut diatas dalam darah Anda. Hasilnya akan digunakan untuk mempertimbangkan dosis obat-obat diatas yang paling tepat untuk Anda.

Penggunaan EXJADE bersama makanan dan minuman

EXJADE tablet dispersibel

EXJADE harus dikonsumsi dalam kondisi perut kosong setidaknya 30 menit sebelum makan, pada waktu yang sama setiap harinya.

Jangan dilarutkan dalam minuman bersoda atau susu.

EXJADE tablet salut selaput

EXJADE dapat dikonsumsi dalam kondisi perut kosong atau dengan makanan ringan (kurang dari 50% kalori dari lemak) pada waktu yang sama setiap harinya.

Kehamilan dan Menyusui

Efek EXJADE terhadap fertilitas belum diketahui.

EXJADE tidak direkomendasikan selama kehamilan kecuali bila sangat dibutuhkan. Jika Anda sedang hamil atau kemungkinan sedang hamil, beritahukan kepada dokter Anda dan berdiskusi dengannya apakah Anda bisa mengonsumsi EXJADE selama kehamilan.

Menyusui tidak direkomendasikan selama pengobatan dengan EXJADE. Beritahukan kepada dokter Anda jika Anda sedang menyusui.

Konsultasikan kepada dokter atau apoteker Anda sebelum Anda mengonsumsi obat-obatan apapun.

Wanita usia produktif

EXJADE dapat menurunkan efektivitas dari kontrasepsi oral atau kontrasepsi tempel (*skin patch*), oleh karenanya Anda berisiko hamil jika Anda hanya menggunakan kontrasepsi oral atau tempel. Anda sebaiknya menggunakan kontrasepsi tambahan atau jenis lainnya untuk mencegah kehamilan.

Mengemudi dan menjalankan mesin

Jika Anda merasa pusing setelah mengonsumsi EXJADE, jangan mengemudi atau menjalankan peralatan atau mesin sampai Anda merasa normal kembali.

Informasi penting tentang bahan yang terkandung dalam EXJADE

EXJADE mengandung laktosa (gula susu). Jika Anda menderita intoleransi berat terhadap laktosa, beritahukan kepada dokter Anda sebelum mengonsumsi EXJADE.

3 Bagaimana cara mengonsumsi EXJADE

Ikuti instruksi yang diberikan oleh dokter Anda secara saksama. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.

Exjade tablet dispersible dan Exjade tablet salut selaput merupakan formulasi yang berbeda dengan zat aktif yang sama; oleh karenanya dosis akan berubah jika Anda berganti dari sediaan tablet dispersible ke tablet salut selaput dan sebaliknya.

Berapa banyak EXJADE yang dikonsumsi

- Dosis EXJADE tergantung dari berat badan pasien. Dokter Anda akan menghitung dosis yang Anda perlukan dan memberitahukan kepada Anda berapa banyak tablet yang harus dikonsumsi per hari.

EXJADE tablet dispersibel

- Dosis umum yang digunakan pada saat awal pengobatan:
  - **20** mg per kilogram berat badan untuk pasien yang menerima transfusi darah rutin.
  - **10** mg per kilogram berat badan untuk pasien yang tidak menerima transfusi darah rutin.

EXJADE tablet salut selaput

Dosis umum yang digunakan pada saat awal pengobatan:

- **14** mg per kilogram berat badan untuk pasien yang menerima transfusi darah rutin.
- **7** mg per kilogram berat badan untuk pasien yang tidak menerima transfusi darah rutin.

Dosis awal yang lebih tinggi atau rendah mungkin dapat direkomendasikan oleh dokter Anda berdasarkan kebutuhan pengobatan individual.

- Berdasarkan respon dari tubuh Anda terhadap pengobatan dengan EXJADE, dokter Anda mungkin akan menyesuaikan pengobatan Anda dengan dosis yang lebih tinggi atau rendah.

EXJADE tablet dispersible

- Dosis harian maksimum:
  - **40** mg per kilogram berat badan untuk pasien yang menerima transfusi darah rutin (Dosis ini dapat dipertimbangkan apabila pengobatan dengan dosis 30 mg per kilogram berat badat tidak efektif terhadap pasien (misalnya: kadar serum feritin selalu diatas 2.500 µg/l dan tidak menunjukan penurunan seiring waktu)
  - **20** mg per kilogram berat badan untuk pasien yang tidak menerima transfusi darah rutin.

EXJADE salut selaput

Dosis harian maksimum:

- **28** mg per kilogram berat badan untuk pasien yang menerima transfusi darah rutin (Dosis ini dapat dipertimbangkan apabila pengobatan dengan dosis 30 mg per kilogram berat badat tidak efektif terhadap pasien (misalnya: kadar serum feritin selalu diatas 2.500 µg/l dan tidak menunjukan penurunan seiring waktu)
- **14** mg per kilogram berat badan untuk pasien yang tidak menerima transfusi darah rutin.

Kapan mengonsumsi EXJADE

EXJADE tablet dispersible

- Exjade tablet dispersible dikonsumsi sehari sekali, setiap hari, pada waktu yang sama.
- Exjade tablet dispersible dikonsumsi dalam keadaan perut kosong.
- Setelah mengonsumsi Exjade tablet dispersible, pasien harus menunggu hingga sekurang-kurangnya 30 menit sebelum mengonsumsi makanan lain.

Konsumsilah Exjade tablet dispersible pada waktu yang sama setiap harinya, ini akan membantu Anda mengingat kapan waktu untuk mengonsumsi tablet Anda setiap harinya.

Bagaimana cara mengonsumsi Exjade tablet dispersible:

- **Masukan** tablet ke dalam segelas air putih, atau jus apel atau jus jeruk (volume air 100 – 200 mL)
- **Aduk** rata sampai tablet larut seluruhnya. Cairan di dalam gelas akan terlihat keruh.

- **Minum** seluruh isi gelas. Tambahkan sedikit air putih atau jus untuk melarutkan obat yang tersisa di dalam gelas dan minum kembali sisanya.

Jangan melarutkan tablet dalam minuman bersoda atau susu.

Jangan mengunyah, mematahkan atau menghancurkan tablet.

Jangan menelan utuh tablet.

Exjade tablet salut selaput

- Exjade tablet salut selaput di konsumsi sekali sehari, pada waktu yang sama setiap harinya dengan bantuan air.
- Tablet dikonsumsi dalam keadaan perut kosong atau dengan makanan ringan.
- Jika Anda tidak dapat menelan tablet secara utuh, Anda dapat menggerusnya. Lalu taburkan ke makanan lembut seperti yogurt atau *apple sauce (apple puree)*. Anda harus langsung mengonsumsi obat tersebut dan jangan menyisakan untuk dikonsumsi pada lain waktu.

Konsumsilah Exjade tablet salut selaput pada waktu yang sama setiap harinya, ini akan membantu Anda mengingat kapan waktu untuk mengonsumsi tablet Anda setiap harinya.

Berapa lama mengonsumsi EXJADE

Lanjutkan mengonsumsi EXJADE setiap hari selama disarankan dokter Anda. Ini merupakan pengobatan jangka panjang yang mungkin dapat berlangsung bulanan bahkan tahunan. Dokter Anda akan memonitor kondisi Anda secara rutin untuk memeriksa apakah pengobatan tersebut sesuai dengan hasil yang diharapkan (Lihat bagian 1: Cara memonitor pengobatan dengan EXJADE).

Hubungi dokter Anda jika Anda memiliki pertanyaan terkait lama konsumsi EXJADE.

Apabila Anda mengonsumsi EXJADE lebih dari yang seharusnya

Apabila Anda mengonsumsi EXJADE lebih dari yang seharusnya, atau orang lain secara tidak sengaja mengonsumsi tablet Anda, segera hubungi dokter Anda atau Rumah Sakit terdekat untuk penanganan segera. Tunjukanlah kemasan tablet tersebut. Tindakan medis mungkin diperlukan. Anda mungkin mengalami efek seperti nyeri abdomen, diare, mual dan muntah, dan gangguan ginjal atau hati yang dapat menjadi serius.

Apabila Anda lupa mengonsumsi EXJADE

Apabila anda melewatkan satu dosis, minum segera setelah Anda ingat pada hari yang sama. Minumlah dosis selanjutnya sesuai jadwal. Jangan mengonsumsi dosis ganda di hari berikutnya untuk menutupi dosis yang telah Anda lewatkan.

Apabila Anda berhenti mengonsumsi EXJADE

Jangan berhenti mengonsumsi EXJADE kecuali diperintahkan dokter Anda. Jika Anda berhenti mengonsumsi, kelebihan zat besi tidak dapat dibuang dari tubuh Anda (lihat bagian “Berapa lama mengonsumsi EXJADE”).

4 Efek samping yang mungkin terjadi

Seperti obat-obatan lainnya, pasien yang diobati dengan EXJADE mungkin mengalami efek samping, meskipun tidak semua pasien mendapatkannya.

HENTIKAN konsumsi EXJADE dan carilah segera pertolongan medis jika Anda atau anak Anda mengalami kondisi di bawah ini:

Gejala yang mungkin merupakan tanda reaksi alergi:

- Sulit bernafas dan sulit menelan
- Pembengkakan pada wajah, bibir, lidah atau tenggorokan.
- Rasa gatal yang parah pada kulit, disertai dengan ruam merah atau bentol.

Beberapa efek samping yang mungkin serius

Jika Anda mengalami efek samping di bawah ini, **hentikan konsumsi obat dan segera beritahukan dokter Anda.**

Tidak umum: *dapat terjadi pada 1 dari 100 orang*

- Muntah darah dan/atau *feses* kehitaman.
- Mulas, nyeri perut atau nyeri pada abdomen terutama setelah menkonsumsi obat (hal ini dapat merupakan tanda maag).
- Penurunan volume pengeluaran urin (hal ini dapat merupakan tanda masalah pada ginjal).
- Jika Anda mengalami kombinasi antara mengantuk, nyeri pada perut bagian kanan atas, dan timbulnya warna kekuningan pada kulit atau mata dan urin yang berwarna gelap (hal ini dapat merupakan tanda masalah pada hati).
- Kehilangan sebagian dari penglihatan Anda.
- Nyeri punggung mendadak atau nyeri pada bagian kanan perut (hal ini dapat merupakan tanda batu empedu).
- Nyeri pada perut bagian atas (pankreatitis).

Jarang: *dapat terjadi pada 1 dari 10.000 orang*

Reaksi kulit parah yang dapat menyebabkan: Ruam kulit, kulit kemerahan, kulit pecah pada daerah sekitar bibir, mata atau mulut, pengelupasan kulit, demam tinggi, gejala flu dan pembesaran kelenjar getah bening.

Tidak diketahui*: frekuensi tidak dapat diestimasi dari data yang tersedia*

- Terjadinya *ulcus* (laserasi/robekan dan lubang) pada dinding perut atau dinding usus yang terasa sakit dan bisa menyebabkan mual.

Efek samping lain yang mungkin terjadi

Efek samping lain termasuk di bawah ini. Jika efek samping dibawah ini menjadi berat segera hubungi dokter atau apoteker Anda.

Sangat umum: *efek samping ini dapat terjadi pada lebih dari 1 dari 10 orang*

- Tes darah urin yang abnormal (peningkatan kadar kreatinin dalam urin).

Umum: e*fek samping ini dapat terjadi pada 1 dari 10 orang*

- Gangguan pada saluran cerna, seperti mual, muntah, diare, nyeri pada perut, kembung, sembelit, dan gangguan pencernaan
- Ruam kulit
- Sakit kepala
- Tes darah hati yang abnormal (peningkatan kadar transaminase dalam darah)
- Gatal
- Kadar protein dalam urin dengan jumlah abnormal

Tidak umum: *efek samping ini dapat terjadi pada lebih dari 1 dari 100 orang*

- Pusing
- Demam
- Penglihatan kabur atau berawan
- Penurunan pendengaran
- Radang tenggorokan
- Pembengkakan pada lengan atau kaki
- Perubahan warna kulit
- Kecemasan
- Gangguan tidur
- Kelelahan

Tidak diketahui: *frekuensi tidak dapat diestimasi dari data yang tersedia*

- Rambut rontok
- Penurunan jumlah sel yang terlibat dalam penyumbatan darah (*Thrombocytopenia*), penurunan jumlah sel darah merah (*anaemia aggravated*), dan penurunan jumlah sel darah putih (*neutropenia*)

Jika Anda mengalami efek samping lain yang tidak disebutkan pada brosur ini, beritahukan segera kepada dokter, apoteker atau tenaga kesehatan Anda.

5 Cara Penyimpanan EXJADE

- Jauhkan dari jangkauan dan penglihatan anak-anak.
- Jangan gunakan EXJADE setelah tanggal kadaluwarsa yang tercantum pada kemasan. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan itu.
- Simpan pada suhu di bawah 30°C.
- Simpan pada kemasan aslinya untuk melindungi dari kelembaban.
- Jangan digunakan jika kemasan rusak atau ada tanda-tanda kerusakan.

Tanyakan kepada apoteker terkait cara pembuangan obat yang tidak lagi Anda gunakan.

6 Informasi lebih lanjut

Kandungan Exjade

EXJADE tablet dispersibel

- Zat aktif EXJADE adalah deferasirox.
- Kandungan lainnya adalah laktosa, *crospovidone, povidone, sodium lauryl sulphate, microcrystalline cellulose*, *silicon dioxide* dan *magnesium stearate*.

EXJADE tablet salut selaput

- Zat aktif EXJADE adalah deferasirox.
- Kandungan lainnya adalah *microcrystalline cellulose; crospovidone; povidone (K30); magnesium stearate; colloidal silicon dioxide; poloxamer 188; coating material: hypromellose; titanium dioxide (E171); polyethylene glycol (4000); talc; FD&C blue #2/indigo carminine aluminum lake (E132).*

Bagaimana bentuk EXJADE

EXJADE tablet dispersibel

EXJADE dijual dalam bentuk tablet dispersibel berwarna keputihan, bulat dan datar. Tiap tablet mengandung 250 mg atau 500 mg deferasirox:

- EXJADE 250 tablet dispersibel mengandung 250 mg deferasirox. Kekuatan 250 mg di cap pada tiap tablet ("J250").
- EXJADE 500 mg tablet dispersibel mengandung 500 mg deferasirox. Kekuatan 500 di cap pada tiap tablet ("J500").

Exjade tablet salut selaput

- Exjade 180 mg tablet salut selaput: tablet salut selaput berbentuk oval berwarna biru dengan sisi bersudut (*beveled edge*), bertanda 'NVR' pada satu sisi dan '180' pada bagian atas diantara garis pada sisi lainnya.
- Exjade 360 mg tablet salut selaput: tablet salut selaput berbentuk oval berwarna biru gelap dengan sisi bersudut (*beveled edge*), bertanda 'NVR' pada satu sisi dan '360' pada bagian atas diantara garis pada sisi lainnya.

Kemasan

Exjade® tablet dispersibel 250mg: Dus, 4 blisters @ 7 tablets, Reg. No.

Exjade® tablet dispersibel 500mg: Dus, 4 blisters @ 7 tablets, Reg. No.

Exjade® tablet salut selaput 180mg: Dus, 3 blisters @ 10 tablets, Reg. No. DKI2257000217B1

Exjade® tablet salut selaput 360mg: Dus, 3 blisters @ 10 tablets, Reg. No. DKI2257000217C1

HARUS DENGAN RESEP DOKTER

Pemegang Ijin Edar

PT. Novartis Indonesia

Pabrik Pembuat

Exjade Tablet Salut Selaput

Dibuat oleh Sandoz S.R.L., Targu Mures, Romania untuk Novartis Pharma AG, Basel, Swiss
Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia

Exjade Tablet Dispersibel

Dibuat oleh Sandoz S.R.L., Targu Mures, Romania untuk Novartis Pharma AG, Basel, Swiss
Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia

Apabila Anda memiliki pertanyaan mengenai obat ini, mohon hubungi dokter atau apoteker Anda.

PIL based on BPL 24-Jul-2019 and change of manufacturing site to Targu Mures