NOVARTIS

Exjade®

Composition
Active substance: Deferasirox
Excipients: Tableting excipients

Pharmaceutical form and quantity of active substance per unit
Dispersible tablets containing 100, 125, 250, 400 or 500 mg deferasirox

Indications / Potential uses
Treatment of transfusion-induced haemosiderosis

Dosage and Administration
The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron overload. The decision to administer iron chelation therapy should take into account the risk-benefit ratio for the individual patient.
The recommended initial dose of Exjade is 20 mg/kg bodyweight once daily.
Exjade should be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day.
Exjade tablets are dispersed by stirring them in a glass of water, non-carbonated (still) apple juice or orange juice (100–200 ml) until a fine dispersion is obtained. After the dispersion has been swallowed, any residue must be redispersed in a small volume of water or juice and swallowed. Exjade tablets must not be chewed, or swallowed in an undispersed form.
It is recommended that in patients who receive regular blood transfusions (more than 8 units of packed red blood cells per year), therapy with Exjade be started after the transfusion of approximately 20 units (equivalent to about 100 ml/kg) of packed red blood cells, and when there is evidence from clinical monitoring that chronic iron overload is present (serum ferritin > 1000 µg/litre or liver iron concentration of > 2 mg Fe/g dry weight).
An initial dose of 30 mg/kg/day may be considered in patients receiving more than 14 ml/kg/month of packed red blood cells (i.e. more than 4 units per month in adults) and in whom a reduction of existing iron exposure is desired.
An initial dose of 10 mg/kg/day may be considered in patients receiving less than 7 ml/kg/month of packed red blood cells (i.e. less than 2 units per month in adults) and in whom the level of iron should neither increase nor decrease.
In patients who already respond well to treatment with deferoxamine, an initial Exjade dose should be considered that numerically corresponds to half the dose of deferoxamine (for example, a patient receiving 40 mg/kg/day deferoxamine on five days per week – or equivalent – could be started on 20 mg/kg/day Exjade).
It is recommended that serum ferritin be monitored once a month, and that the dose of Exjade be adjusted in steps of 5 to 10 mg/kg/day every 3 to 6 months. In patients not adequately controlled on daily doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 µg/litre, and not showing a decreasing trend over time), daily doses of up to 40 mg/kg may be considered.
Doses exceeding 40 mg/kg/day are not recommended because there is only limited experience with doses above this level.
Dose reductions, in steps of 5 to 10 mg/kg, should be considered in patients whose serum ferritin levels have reached the target (usually between 500 and 1000 µg/litre) in order to maintain serum ferritin levels within the target range.
If serum ferritin is below 500 µg/litre at several consecutive determinations, treatment should be interrupted. Urinary iron excretion is not an appropriate parameter for monitoring of treatment (see **Pharmacokinetics**).
As with other iron chelator treatment, the risk of toxicity with Exjade may be increased when excessively high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see **Warnings and Precautions**).

Special dosage recommendations
Elderly patients, children and adolescents
No special dosage recommendations.
Exposure in children between 2 and < 6 years of age is lower than in adults. 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 dose titration. Deferasirox is not recommended for use in children below 2 years of age due to insufficient data on safety and efficacy (see **Pharmacokinetics**).

Patients with renal impairment
Exjade has not been studied in patients with renal impairment. Exjade must be used with caution in patients with elevated serum creatinine levels. Exjade is contraindicated in patients with creatinine clearance < 60 ml/minute.
For patients with renal impairment and creatinine clearance ≥ 60 ml/minute, the starting doses are the same as those described above. For response monitoring and dose adjustment, (see **Warnings and Precautions**).

Patients with hepatic impairment
Exjade has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as described above. Hepatic function should be monitored in all patients before initiating treatment, then every 2 weeks during the first month of treatment and monthly thereafter (see **Warnings and Precautions**).

Contraindications
– Known hypersensitivity to the active substance or any of the excipients.
– Creatinine clearance < 60 ml/minute.

Warnings and Precautions
Exjade has not been studied in patients with renal or hepatic impairment and must be used with caution in such patients. Exjade treatment has been initiated only in patients with serum creatinine within the age-appropriate normal range, and with baseline liver transaminase levels up to not more than 5 times the upper limit of the normal range (ULN). Deferasirox is minimally excreted via the kidney (8% of the dose). It is principally eliminated by glucuronidation and is minimally metabolized (about 8%) by oxidative cytochrome P450 enzymes (see **Pharmacokinetics**). Exjade should be used with caution in patients with congenital disturbances of glucuronidation.

Kidneys
During clinical studies, dose-dependent increases in serum creatinine were observed in some patients treated with Exjade. In one such clinical study, serum creatinine increases of > 33% were noted at two consecutive measurements in 38% of patients taking deferasirox (Exjade) and 14% of patients taking deferoxamine. Cases of acute renal failure, some with fatal outcome, have been reported during postmarketing use of Exjade (see **Adverse effects**). While it is true that a connection between Exjade and renal dysfunction cannot be fully ruled out in the cases with a fatal outcome, the fatal outcome is probably a consequence of the underlying condition of these severely ill patients. The fact that there was an improvement in renal function in most of the non-fatal cases following withdrawal of treatment indicates an involvement of Exjade in the acute renal failure. It is recommended that serum creatinine be measured twice before initiating therapy. Serum creatinine should be monitored weekly during the first month of treatment, or after treatment modifications, and thereafter at monthly intervals. Tests for proteinuria should be performed monthly. There may be an increased risk of complications in patients with pre-existing renal conditions or in patients who are receiving medicinal products that depress renal function. Care must be taken to ensure adequate hydration in patients with diarrhoea or vomiting.
In adult patients, the dose of Exjade may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by > 33% above the average of the two pretreatment measurements is seen in two consecutive measurements and cannot be attributed to other causes.
It should be noted that such dose adjustments because of creatinine increases were necessary in 11% of patients in clinical studies. In most patients requiring dose reduction, serum creatinine did not return to baseline. In 60% of patients with dose reduction, serum creatinine remained elevated by > 33%, with no further increase.
Treatment with Exjade should be discontinued if the increase in serum creatinine is progressive. Treatment with Exjade should also be discontinued if serum creatinine remains in excess of 33% or if creatinine clearance falls below the age-appropriate normal range. Resumption of treatment is determined by the individual clinical situation.
In children, the dose should be reduced by 10 mg/kg if serum creatinine rises above the age-appropriate upper limit of normal at two consecutive measurements.

Liver
Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%) in clinical studies. There have been postmarketing reports of hepatic failure with Exjade. Most cases of hepatic failure involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure, and fatal outcomes were reported in some of these patients (see **Adverse effects**).
Serum transaminases, bilirubin and alkaline phosphatase should be monitored before initiating treatment, then every 2 weeks during the first month of treatment and monthly thereafter. Exjade should be discontinued if there is a persistent and progressive increase in serum transaminase levels that can not be attributed to other causes. Once the cause of the liver function test abnormalities has been clarified, or after a return to normal levels, cautious reinitiation of Exjade treatment at a lower dose, followed by gradual dose escalation, may be considered.

Gastrointestinal effects
Gastrointestinal irritation may occur during treatment with Exjade. Upper gastrointestinal ulcers and haemorrhage have been reported in patients – including children and adolescents – treated with Exjade. Multiple ulcers have been observed in some patients (see **Adverse effects**). Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulcers and haemorrhage during Exjade therapy. Further evaluation and appropriate treatment should be initiated immediately if a serious gastrointestinal adverse event is suspected.
Caution is required in patients taking Exjade in combination with medicinal products that have known ulcerogenic potential (such as NSAIDs, corticosteroids, or oral bisphosphonates) and in patients using anticoagulants (see **Interactions**).

Skin disorders
Skin rashes may appear during Exjade treatment. For rashes of mild to moderate severity, Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. Interruption of treatment may be necessary if the rash is more severe. Exjade may be reintroduced at a lower dose, followed by gradual dose escalation, after resolution of the rash. In severe cases, Exjade may be reintroduced in combination with a short course of oral corticosteroids.

Hypersensitivity reactions
Rare cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema), occurring in most cases within the first month of treatment, have been reported in patients treated with Exjade (see **Adverse effects**). In the event of severe reactions, the usual appropriate medical measures must be taken and treatment with Exjade must be discontinued.

Eyes and ears
Disturbances of hearing (decreased hearing) and vision (lens opacities) have been reported with Exjade treatment (see **Adverse effects**). Auditory and ophthalmic testing (including fundoscopy) are recommended before the start of Exjade treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or withdrawal of Exjade should be considered.

Haematological disorders
There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with Exjade (see **Adverse effects**). Most of these patients had pre-existing haematological disorders potentially associated with bone marrow failure. The relationship of these episodes to treatment with Exjade is uncertain. In line with the standard clinical management of such haematological disorders, peripheral blood counts should be regularly performed. Interruption of treatment with Exjade should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with Exjade may be considered once the cause of the cytopenia has been elucidated, and an association with Exjade has been excluded with adequate certainty.

General precautions
As with other iron chelator treatment, the risk of toxicity with Exjade may be increased when excessively high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
As a general precautionary measure, bodyweight and longitudinal growth should be monitored at regular intervals (every 12 months) in paediatric patients.
No data are available at present on the frequency of sickle cell crises, as compared with the frequency of such crises in patients not receiving chelator therapy.
Exjade has not been studied in patients with aluminium overload and should not be used in this indication.
Exjade must not be combined with other iron chelator therapies as the safety of such combinations has not been established.
Exjade tablets contain lactose (1.1 mg lactose for each mg of deferasirox). This medicinal product is not recommended in patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Interactions
Concomitant administration of Exjade and antacids containing aluminium has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron, an interval of 2 hours should be observed between ingestion of Exjade tablets and ingestion of antacids containing aluminium.
In a study in healthy volunteers, concomitant administration of Exjade and midazolam (a CYP3A4 probe substrate) resulted in a 17% decrease in midazolam exposure. This effect may be more pronounced in clinical practice. Caution is therefore also required when combining deferasirox with substances metabolized by CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents) due to a possible decrease in efficacy.
In a study in healthy volunteers, concomitant administration of Exjade (single dose of 30 mg/kg) and repeated daily doses of 600 mg rifampicin (a potent inducer of UDP-glucuronosyltransferase [UGT]) resulted in a 44% decrease in deferasirox exposure (90% CI: 37%–51%). Concomitant use of Exjade with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may thus reduce the efficacy of Exjade, and an increase in the dose of Exjade should be considered, based on therapeutic response.

In a study in healthy volunteers, concomitant administration of Exjade (single dose of 30 mg/kg) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) resulted in increases of 131% (90% CI: 103%–164%) and 62% (90% CI: 42%–84%), respectively, in repaglinide AUC and C_{max}. Glucose levels should be closely monitored if Exjade and repaglinide are administered concomitantly. Caution is required when using Exjade in combination with other CYP2C8 substrates, such as paclitaxel.
No interaction was observed between Exjade and digoxin.
The concomitant administration of Exjade and vitamin C has not been formally studied.
Interactions between Exjade and gallium contrast media have not been studied. It is known that the results of gallium-67 imaging may be distorted by the iron chelator deferoxamine due to chelation of gallium-67. It is therefore recommended that Exjade therapy be interrupted at least five days before gallium-67 scintigraphy.
Concomitant administration of Exjade with medicinal products that have known ulcerogenic potential (such as NSAIDs, corticosteroids or oral bisphosphonates) and administration of Exjade in patients receiving anticoagulants may increase the risk of gastrointestinal irritation (see **Warnings and Precautions**).

Pregnancy and Lactation

Pregnancy

There have been no controlled clinical studies of the use of Exjade during pregnancy. Studies in animals have shown some reproductive toxicity at maternally toxic doses. It is therefore recommended that Exjade should not be used during pregnancy unless absolutely necessary.

Lactation

In animal studies, deferasirox was rapidly and extensively secreted into the milk. No effect on the offspring was noted. It is not known if deferasirox passes into human milk. Breastfeeding is not recommended during treatment with Exjade.

Effects on ability to drive and use machines

There have been no studies of the effects of Exjade on the ability to drive or use machines. Patients experiencing the uncommon adverse effect of dizziness should exercise caution when driving or operating machinery (see **Adverse effects**).

Adverse effects

The adverse effects most frequently reported during long-term treatment with Exjade in adult and paediatric patients were 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 and generally transient. They usually resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients. They are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see **Warnings and Precautions**).
Elevations in liver transaminases were reported in about 2% of patients. They were not dose-dependent, and most of the patients in question already had elevated transaminase levels prior to treatment with Exjade. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). There have been postmarketing reports of hepatic failure with Exjade. Most cases of hepatic failure involved patients with major comorbidities, including liver cirrhosis and multi-organ failure, and fatal outcomes were reported in some cases.
As with other iron chelators, there have been uncommon reports of high-frequency hearing loss and lens opacities (early cataracts) in patients treated with Exjade (see **Warnings and Precautions**).
The following adverse effects have been reported in clinical studies following treatment with Exjade. Adverse effects are listed below in decreasing order of frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10 000). Within each frequency grouping, adverse effects are listed in the order of decreasing severity.

Adverse effects from clinical studies:

Psychiatric disorders
Uncommon: Anxiety, sleep disturbances.

Nervous system disorders
Common: Headache.
Uncommon: Dizziness.

Eye disorders
Uncommon: Early cataract, maculopathy.
Rare: Optic neuritis.

Ear and labyrinth disorders
Uncommon: Hearing loss.

Gastrointestinal disorders
Common: Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia.
Uncommon: Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, pharyngitis.
Rare: Oesophagitis.

Hepatobiliary disorders
Common: Elevated transaminases.
Uncommon: Hepatitis, cholelithiasis.

Skin disorders
Common: Rash, pruritus.
Uncommon: Pigmentation disorder.

Renal and urinary disorders
Common: Proteinuria, elevated serum creatinine (> ULN but < 2 × ULN).
Uncommon: Renal tubulopathy (Fanconi's syndrome).

General disorders
Uncommon: Fever, oedema, fatigue.

Spontaneously reported adverse effects are reported voluntarily, and it is therefore not always possible to precisely establish frequency or a causal relationship to treatment.

Adverse effects, from spontaneous reports:

Immune system disorders
Hypersensitivity reactions (including anaphylaxis, angioedema, urticaria).

Hepatic disorders
Hepatic failure.

Skin disorders
Leucocytoclastic vasculitis, urticaria.

Renal and urinary disorders
Cases of acute renal failure, some with fatal outcome, have been described (see **Warnings and Precautions**).

Blood and lymphatic system disorders
There have been postmarketing reports (both spontaneous and from clinical studies) of cytopenias – including neutropenia, thrombocytopenia and pancytopenia – in patients treated with Exjade. Most of these patients had preexisting haematological disorders that are frequently associated with bone marrow failure (see **Warnings and Precautions**). The relationship of these episodes to treatment with Exjade is uncertain.

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 without long-term consequences after a dose interruption. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients have been tolerated, with only mild nausea and diarrhoea noted. Single doses of up to 40 mg/kg have been well tolerated in healthy subjects.
Possible acute signs of overdose are nausea, vomiting, headache and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment.

Properties and Actions

ATC code: V03AC03

Pharmacodynamics

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 in the faeces. Deferasirox also has a lower affinity for aluminium and a much lower affinity for zinc and copper.
Exjade produced similar results in patients with transfusion-induced haemosiderosis associated with a variety of underlying diseases, such as beta-thalassaemia, sickle cell anaemia, myelodysplastic syndrome or Diamond-Blackfan syndrome.
Daily treatment with Exjade 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 total body iron. On average, liver iron concentration was reduced by 0.4 and 8.9 mg Fe/g liver (biopsy dry weight), respectively, and serum ferritin was reduced by 36 and 926 µg/litre, respectively. The quotients of iron excretion : iron intake were, respectively, 1.02 (net iron balance) and 1.67 (net iron removal). Trends in serum ferritin can be used to monitor response to therapy.

Pharmacokinetics

Absorption

Deferasirox is absorbed following oral administration, with a median time to maximum plasma concentrations (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from Exjade tablets is 73.5 ± 12.8%. Total exposure (AUC) was approximately doubled when tablets were taken along with a high-fat breakfast (fat content > 50% of calories) and was about 50% higher when tablets were taken along with a standard breakfast. Bioavailability (AUC) was moderately elevated (by 13–25%) when deferasirox was taken 30 minutes before meals with normal or high fat content. The total exposure (AUC) to deferasirox when taken after dispersion of tablets in orange juice or apple juice was equivalent to the exposure after dispersion in water (relative AUC ratios of 103% and 90%, respectively).

Distribution

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

Metabolism

Glucuronidation, with subsequent biliary excretion, is the main metabolic pathway for deferasirox. Deconjugation of glucuronides 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 is negligible.

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, 6% as hydroxylated deferasirox). The terminal elimination half-life ($t_{½}$) ranges from 8 to 16 hours.

Linearity

The pharmacokinetics of deferasirox are not dose-proportional.
The C_{max} and AUC_{0-24h} of deferasirox increase approximately linearly with the dose under steady-state conditions.
Upon multiple dosing, exposure increased by an accumulation factor of 1.3 to 2.3.

Pharmacokinetics in special patient populations

Overall exposure to deferasirox in adolescents (12 to 18 years) and children (2 to 11 years) after single and multiple doses was lower than in adult patients. In children under 6 years of age, exposure was about 50% lower than in adults.
There was no clinically relevant difference between females and males in the apparent clearance of deferasirox.
The pharmacokinetics of deferasirox have not been studied in elderly patients (aged 65 years or older).

Renal and hepatic impairment

The pharmacokinetics of deferasirox have not been studied in patients with renal or hepatic impairment.

Preclinical data

The main findings with chronic therapy were nephrotoxicity, bile duct changes and lens opacity (cataracts). Similar findings were observed in neonatal and juvenile animals.
In vitro genotoxicity studies were either negative (Ames test, chromosome aberration test in human lymphocytes) or positive (V79 screen). *In vivo*, lethal doses of deferasirox caused the formation of micronuclei in the bone marrow of non-iron-overloaded rats. However, no such cytotoxic effects were observed in the liver or bone marrow in iron-overloaded rats. Deferasirox was not carcinogenic when given to rats in a two-year study, or to heterozygous transgenic p53+/- mice in a six-month study.
Reproductive toxicity was assessed in rats and rabbits. Deferasirox was not teratogenic, but caused an increased incidence of skeletal changes and stillbirths in rats given high doses that were severely toxic to the non-iron-overloaded mothers. Deferasirox did not cause other effects on fertility or reproductive function.

Other information

Incompatibilities

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

Shelf-life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

See folding box.

Manufacturer

See folding box

Pack sizes

Country specific pack sizes

Information last revised

March 2009

Approval date (text)

17 March 2009

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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