My Exjade/Jadenu (deferasirox) Handbook

Patient handbook

NAME DATE

This document has been approved by Saudi Food and Drug Authority (SFDA).

EU RMP V 16.2 / Feb 2021

Table of Contents

Exjade/Jadenu (deferasirox) Handbook

Objective

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks.

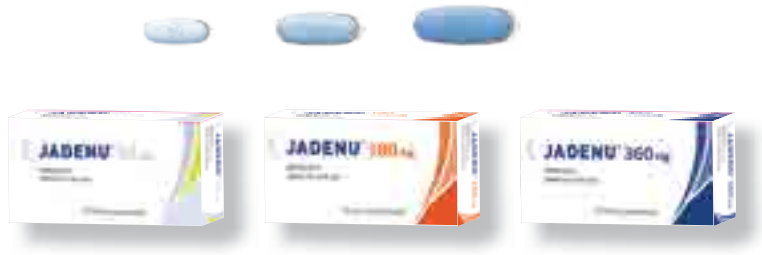
What is Exjade/Jadenu (deferasirox) used for?

This handbook contains important information about Exjade/Jadenu (deferasirox) . You'll learn about taking Exjade/Jadenu (deferasirox) the right way, depending on which form your doctor prescribed, as well as about monitoring your treatment, possible side effects, and taking other medicines while on Exjade/Jadenu (deferasirox) .

Exjade/Jadenu (deferasirox) is available in multiple forms. Each has a specific shape and color and is taken differently

It is important to take your medicine as directed by your physician.

1) Jadenu (deferasirox) film-coated tablets are blue, oval tablets. They may be swallowed whole on an empty stomach or with a light meal. If you are unable to swallow whole tablets, Jadenu (deferasirox) film-coated tablets may be crushed and sprinkled onto soft food.



2) Exjade(deferasirox) dispersible tablets are white to slightly yellow, round tablets. They must be dissolved in liquid and taken on an empty stomach.

Tablets displayed are not actual size.

What is deferasirox (Exjade/Jadenu)?

Exjade/Jadenu (deferasirox) helps to remove excess iron in the body. Because of this, it is known as an “iron chelator” or “chelation agent.”

Read this material carefully before prescribing/dispensing/administering the produc

Why was I prescribed Exjade/Jadenu (deferasirox) ?

Many kinds of conditions need blood transfusions. Some of these are:

- β-thalassemia major
- Sickle cell disease, or SCD
- Lower-risk myelodysplastic syndromes, or MDS
- Other anemias

If you have one of these conditions, you’ve probably received several blood transfusions. Transfusions have the healthy red blood cells your body needs and can help you feel better.

Every transfusion you are given contains iron. Iron is important because red blood cells use it to carry oxygen around your body. However, the body does not have its own way of removing extra iron.

The amount of iron builds up with each transfusion, and this extra iron in your body, may lead to a condition called **chronic iron overload**. Too much iron can be harmful and damage organs like your heart and liver.

It is important to remove this extra iron to keep your iron at a safe, healthy level.

How does Exjade/Jadenu (deferasirox) work?

Exjade/Jadenu (deferasirox) works by a process called **“chelation”** (key-lay-shun).

After you swallow Exjade/Jadenu (deferasirox) , Exjade/Jadenu (deferasirox) enters your blood and” “captures” extra iron available.

What is Exjade/Jadenu (deferasirox) used for?

Exjade/Jadenu (deferasirox) is used to treat chronic iron overload caused by frequent bloodtransfusions in patients aged 6 years and older with a blood disorder called b-thalassemia major.

Exjade/Jadenu (deferasirox) is also used to treat chronic iron overload when a medicationcalled deferoxamine should not be used or did not improve outcomes in patients with b-thalassemia major and iron overload caused by infrequent blood transfusions, in patients with other types of blood disorders called anemias, and in children aged 2 to 5 years.

Exjade/Jadenu (deferasirox) is also used when deferoxamine should not be used or did not improve outcomes in patients aged 10 years or older who have iron overload associated with their thalassemia syndromes, but who are nottransfusion dependent.

How do I take Jadenu (deferasirox) film-coated tablet?

What dose will I take?

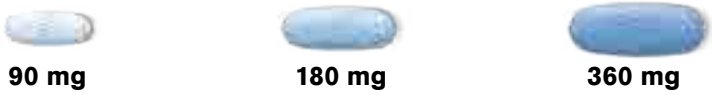
Your prescribed dose of Jadenu (deferasirox) film-coated tablets is based on your weight, current iron level, liver and kidney function, and how often you get transfusions.

If you are switching from Exjade (deferasirox) dispersible tablets to Jadenu (deferasirox) film-coated tablets, you will need a lower dose. If you are changing from a different medication (such as deferoxamine) to Jadenu (deferasirox) film-coated tablets, your doctor may choose your Jadenu (deferasirox) dose based on how much of the previous medication you were taking.

Which tablet(s) will I take?

Jadenu (deferasirox) film-coated tablets comes in different tablet sizes, and you may need to take more than one. Your doctor will tell you how many tablets and which size(s) you should take each day.

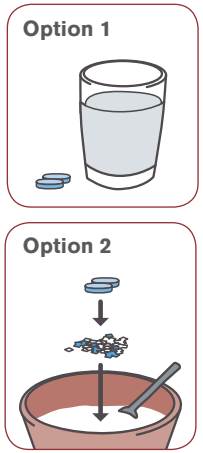
Jadenu (deferasirox) film-coated tablets



90 mg **180 mg** **360 mg**

Tablets displayed are not actual size.

How and when to take Exjade/Jadenu (deferasirox) film-coated tablets



Jadenu (deferasirox) film-coated tablets should be swallowed whole with some water. If you're unable to swallow whole tablets, you can crush the Jadenu (deferasirox) film-coated tablets and sprinkle the full dose onto a small amount of soft food, such as yogurt or applesauce (puréed apple).
You should immediately and completely consume the entire dose and not store any for future use.

Jadenu (deferasirox) film-coated tablets should be taken once a day. You should ideally take your Jadenu (deferasirox) at the same time each day. Jadenu (deferasirox) film-coated tablets may be taken on an empty stomach or with a light meal.

What if I forget to take my dose?

If you miss taking a dose of Exjade/Jadenu (deferasirox) , you should still take it when you
remember, even if it is later in the day. Take your next dose as scheduled.

Do not take a double dose on the next day to make up for the forgotten tablet(s).

What if I take more Jadenu (deferasirox) tablets than I should?

If you have taken too much Jadenu (deferasirox) , or if someone else accidentally takes your tablets, contact your doctor or hospital for advice straight away.
Show the doctor the pack of tablets. Urgent medical treatment may be necessary. You may experience effects such as abdominal pain, diarrhoea, nausea and vomiting and kidney or liver problems that can be serious.

How do I take Exjade (deferasirox) dispersible tablets?

What dose will I take?

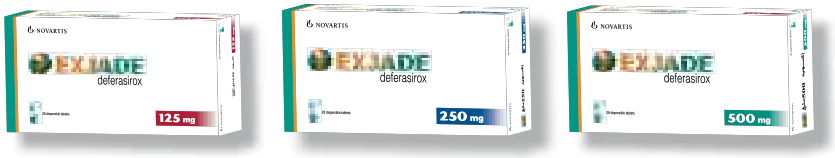
Your prescribed dose of Exjade (deferasirox) dispersible tablets is based on your weight, current iron level, liver and kidney function, and how often you get transfusions. If you are changing to Exjade (deferasirox) dispersible tablets from a different medication (such as deferoxamine), your doctor may choose your Exjade (deferasirox) dose based on how much of the previous medication you were taking.

Which tablet(s) will I take?

Exjade (deferasirox) dispersible tablets come in different tablet sizes, and you may need to take more than one. Your doctor will tell you how many tablets and which size(s) you should take each day.

125 mg **250 mg** **500 mg**

Tablets shown actual size.



When will I take Exjade (deferasirox) dispersible tablets?

You should take your Exjade (deferasirox) dispersible tablets once a day and at the same time each day. Taking Exjade (deferasirox) at the same time each day will help you remember when you should take your tablet. Exjade (deferasirox) dispersible tablets should be taken on an empty stomach at least 30 minutes before eating.

How do I store Exjade (deferasirox) ?

You should store your Exjade (deferasirox) tablets in their original packaging to protect against moisture.

Steps to take Exjade (deferasirox) dispersible tablets

Step 1:
DROP your Exjade (deferasirox) dispersible tablet(s) into a glass of orange juice, apple juice, or water. You can also use the Exjade (deferasirox) mixer bottle. Make sure that you use the exact amount of liquid directed by your doctor.

Step 2:
STIR until the Exjade (deferasirox) tablet(s) completely dissolve. The liquid in the glass will look cloudy and the consistency of the mixture may be thick.

Step 3:
DRINK all of the Exjade (deferasirox) mixture immediately. Then add a little water or juice to what is left in the glass, swirl the liquid around and drink that, too.

Do not chew or swallow tablets whole. Do not break or crush the tablets.

Do not dissolve your Exjade (deferasirox) dispersible tablets in fizzy drinks or milk.

What if I forget to take my dose?

If you miss taking a dose of Exjade (deferasirox) , you should still take it when you remember, even if it is later in the day. Take your next dose as scheduled.

Do not take a double dose on the next day to make up for the forgotten tablet(s).

What if I take more Exjade (deferasirox) tablets than I should?

If you have taken too much Exjade (deferasirox) , or if someone else accidentally takes your tablets, contact your doctor or hospital for advice straight away. Show the doctor the pack of tablets. Urgent medical treatment may be necessary. You may experience effects such as abdominal pain, diarrhoea, nausea and vomiting and kidney or liver problems that can be serious.

How will my treatment be monitored?

While taking Exjade/Jadenu (deferasirox) , you will have regular laboratory tests. These tests will monitor how you are responding to treatment. Your doctor may adjust your Exjade/Jadenu (deferasirox) dose up or down based on these tests.

Test	Before starting Exjade/Jadenu (deferasirox)	Every month	Once per year
Iron Serum ferritin	✓	✓	
Kidneys Serum creatinine	✓ This blood test will be taken **twice** before starting Exjade/Jadenu (deferasirox)	✓ For the first month and in the first month after any changes in dose, you will be tested once per week; then once per month	
Creatinine clearance	✓	✓ For the first month and in the first month after any changes in dose, you will be tested once per week; then once per month	
Liver (Serum transaminases, bilirubin, alkaline phosphatase)	✓	✓ For the first month, you will be tested every 2 weeks; then once per month	
Urine (Protein in urine)	✓	✓	
Hearing and vision	✓		✓
Pediatric patients: Assess body development (eg, your weight, sexual development, and how much you grow per year)	✓		✓

Your doctor may also

- Use a test called magnetic resonance imaging, or **MRI**, to check iron levels in your heart or liver
- Perform a **biopsy** of your kidneys if he/she suspects kidney problems

Does Exjade/Jadenu (deferasirox) have side effects?

Like all medicines, Exjade/Jadenu (deferasirox) can have side effects. However, not all patients experience them. The most frequent side effects are mild to moderate and usually go away once you get used to treatment. This can take a few days or weeks.

Common side effects include nausea, vomiting, diarrhea, pain in the abdomen, bloating, constipation, indigestion, skin rash, headache, and itching.

Your kidney and liver function will be tested before you start Exjade/Jadenu (deferasirox) and will be checked regularly during treatment. (See table on previous page.)

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

These side effects are uncommon or rare. Stop taking this medicine and tell your doctor right away if you experience any of the following:

- Severe rash or difficulty breathing and dizziness, or swelling mainly of the face and throat (signs of severe allergic reaction),
- Rash, red skin, blistering of lips, eyes or mouth, skin peeling, high fever, flu-like symptoms, enlarged lymph nodes, (signs of severe skin reactions);
- Marked decrease in the amount of urine your body produces (sign of kidney problem);
- Vomiting blood and/or have black stools;
- A combination of drowsiness, upper-right abdominal pain, yellowing or increased yellowing of your skin or eyes and dark urine (signs of liver problems);
- If you experience difficulty thinking, remembering information, or solving problems, being less alert or aware or feeling very sleepy with low energy (potential signs of a high level of ammonia in your blood, which may be associated with liver or renal problems and lead to a change in your brain function)
- Frequent abdominal pain, particularly after eating or taking Exjade/Jadenu (deferasirox) ;
- Severe upper stomach pain;
- Frequent heartburn;
- Partial vision loss

Remember: Always tell your health care provider about any side effects you experience. If you have any serious side effects, STOP taking your medication and contact your doctor immediately.

For more details on side effects and serious side effects, please see the Patient Leaflet.

What about other medicines that I also need to take for my health?

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicine you take without a prescription. Your doctor may need to do laboratory tests to monitor these medicines.

Important medicines to tell your doctor about include, in particular:

- Other iron chelators, which must not be taken with Deferasirox
- Antacids (medicines used to treat heartburn) containing aluminum, which should not be taken at the same time as Deferasirox
- Cyclosporine (used to prevent the body from rejecting a transplanted organ or for other conditions, such as rheumatoid arthritis or atopic dermatitis)
- Simvastatin (used to lower cholesterol)
- Certain painkillers or anti-inflammatory medicines (eg, aspirin, ibuprofen, corticosteroids)
- Oral bisphosphonates (used to treat osteoporosis)
- Anticoagulant medicines (used to prevent or treat blood clotting)
- Hormonal contraceptive agents (birth control medicines)
- Bepridil (used as a treatment for heart problems and migraines)
- Ergotamine (used as a treatment for migraine)
- Repaglinide (used to treat diabetes)
- Rifampicin (used to treat tuberculosis)
- Phenytoin, phenobarbital, carbamazepine (used to treat epilepsy)
- Ritonavir (used in the treatment of HIV infection)
- Paclitaxel (used in cancer treatment)
- Theophylline (used to treat respiratory diseases such as asthma)
- Clozapine (used to treat psychiatric disorders such as schizophrenia)
- Tizanidine (used as a muscle relaxant)
- Cholestyramine (used to lower cholesterol levels in the blood)
- Midazolam (used as a sedative and to treat anxiety and amnesia)
- Busulfan (used as a treatment prior to transplantation in order to destroy the original bone marrow before the transplant)

Contraception

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

My progress with Exjade/Jadenu (deferasirox)

My treatment goal

The goal of Exjade/Jadenu (deferasirox) treatment is to have a healthy amount of iron in your
body. Each month you will visit your doctor to track your progress toward your **treatment goal**.

Your doctor will set your treatment goals based on a blood test called serum ferritin (SEER-um FAIR-it-in), or **SF**, test. This test tells your doctor how much iron is in your body. Your doctor will want to either lower your SF level or keep it where it is.

My dose

Your doctor may decide to change your dose based on your SF level, other laboratory tests, or how often you get transfusions.

After taking Exjade/Jadenu (deferasirox) for 3 to 6 months, check with your doctor that you are making progress as planned. If you are not, ask your doctor about his/her plan for helping you reach your treatment goal.

Between each visit

Other important events may occur between doctor visits. You should keep a record of them and share them with your doctor. They include:

- Side effects
- Other medicines
- Any deviation from the prescribed dosage

My background information

Your background information is helpful for both you and your doctor when planning your treatment with Exjade/Jadenu (deferasirox). Ask your doctor if you need help answering these questions.

General information

First name _____

Last name _____

Date of birth _____

Diagnosis _____

Have I been given transfusions? If so, how many and how often?

_____

_____

Do I have any other health issues?

_____

_____

Am I taking any medicine right now for other health issues?

_____

_____

Do I have any allergies?

_____

_____

Starting Exjade/Jadenu (deferasirox)

You can start tracking your progress once your doctor decides on your goal SF level and dose of Exjade/Jadenu (deferasirox) . Work with your doctor to fill in your treatment goals and other information, below.

Date: _____ **My current SF level:** _____

My treatment goal is to:

Reduce my SF level to

_____

My weight:

_____

My Exjade/Jadenu (deferasirox) dosing regimen

I am taking

☐ Jadenu (deferasirox) film-coated tablets

☐ Exjade (deferasirox) dispersible tablets

- How many tablets will I take each day?

If Jadenu (deferasirox) film-coated tablets:

☐ I can swallow my tablets whole

☐ I will crush my tablets and sprinkle them on a soft food such as yogurt or applesauce (puréed apple) and eat it immediately

- When will I take my medication each day?

_____

Notes: Write down any notes or questions from your visit.

_____

_____

_____

_____

_____

_____

JADENU®

Important note: Before prescribing, consult full prescribing information.

Presentation:

Jadenu® film-coated tablets

Film-coated tablets containing 90 mg, 180 mg or 360 mg of deferasirox.

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

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

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

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

Dosage: Transfusional iron overload

♦**Starting daily dose:**

Jadenu film-coated tablets

Recommended initial daily dose is 14 mg/kg body weight; consider 21 mg/kg for patients receiving >14 mL/kg/month of packed red blood cells (>4 units/month), and for whom the objective is the reduction of iron overload; consider 7 mg/kg for patients receiving <7 mL/kg/month of packed red blood cells (<2 units/month), and for whom the objective is the maintenance of the body iron level**;** for patients already well-managed on treatment with deferoxamine, consider a starting dose of Jadenu that is numerically one third that of the deferoxamine dose. For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Jadenu, the dose of Jadenu should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet.

♦50% starting dose reduction in moderate hepatic impairment (Child-Pugh B). Should not be used in severe hepatic impairment (Child-Pugh C).

♦**Monthly monitoring of serum ferritin** for assessing patient's response to therapy.

♦**Dose adjustment:**

Jadenu film-coated tablets

If necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 3.5 to 7 mg/kg. In patients not adequately controlled with doses of 21 **mg/kg, doses of up to** 28 **mg/kg may be considered. In patients whose serum ferritin level has reached the target (usually between 500 and 1000 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. Jadenu should be interrupted if serum ferritin falls consistently below 500 micrograms/L.

♦**Maximum daily dose:**

Jadenu film-coated tablets

The maximum daily dose of film-coated tablets or granules is 28 mg/kg body weight.

Dosage: Non-transfusion-dependent thalassemia syndromes and iron overload

♦**Starting daily dose:**

Jadenu film-coated tablets

Recommended initial daily dose is 7 mg/kg body weight. 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. For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Jadenu, the dose of Jadenu should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet.

♦**Dose adjustment:**

Jadenu film-coated tablets

Should be considered every 3 to 6 months in steps 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. 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.

♦50% starting dose reduction in moderate hepatic impairment (Child-Pugh B). Should not be used in severe hepatic impairment (Child-Pugh C).

♦**Maximum daily dose:**

Jadenu film-coated tablets

The maximum daily dose of film-coated tablets or granules is 14 mg/kg body weight.

Administration:

Jadenu film-coated tablets

The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, Jadenu 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. Jadenu 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.

Contraindications:

♦Hypersensitivity to deferasirox or to any of the excipients.

♦Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal. ♦ Combination with other iron chelator therapies as the safety of such combinations has not been established

Women of child-bearing potential, pregnancy, breast-feeding and fertility: ♦**Pregnancy:** No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. As a precaution, it is recommended that Jadenu not be used during pregnancy unless clearly necessary.

♦**Breast-feeding:** It is not known if deferasirox is secreted into human milk. Breast-feeding while taking Jadenu is not recommended.

♦**Fertility:** Jadenu did not affect fertility or reproduction in rat studies even at toxic doses.

Warnings and precautions:

♦Caution in elderly patients due to a higher frequency of adverse reactions.

♦Caution 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. Monthly monitoring of creatinine clearance, serum creatinine and proteinuria: dose reduction may be needed in some cases of non-progressive increase in serum creatinine; Jadenu should be interrupted if serum creatinine shows a progressive rise beyond the age-appropriate upper limit of normal. More frequent creatinine monitoring recommended in patients with an increased risk of renal complications. Rare reports of acute renal failure, some of which required dialysis or with fatal outcome. Reports of renal tubulopathy mainly in children with beta-thalassemia and serum ferritin levels <1,500 microgram/L.

♦Not recommended in patients with severe hepatic impairment (Child-Pugh C). Monitoring of serum transaminases, bilirubin and alkaline phosphatase: before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. Jadenu should be interrupted if persistent and progressive unattributable increase in serum transaminases levels. Post-marketing cases of hepatic failure have been reported.

♦Gastrointestinal (GI) irritation may occur. Upper GI ulceration and hemorrhage have been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. There have been reports of ulcers complicated with GI perforation (including fatal outcome). There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 x 10^9/L.

♦Severe cutaneous adverse reactions (SCARs) have been reported. Patients should be advised of the signs and symptoms of SCARs and be closely monitored. If any SCAR is suspected Jadenu should be discontinued immediately and should not be reintroduced.

♦Skin rashes: Jadenu should be interrupted if severe rash develops.

♦Discontinue if severe hypersensitivity reaction occurs. Jadenu should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

♦Annual ophthalmological/audiological testing.

♦Should not be used during pregnancy unless clearly necessary.

♦Not recommended when breast-feeding.

♦Product contains lactose.

Interactions:

♦Should not be taken with aluminium-containing antacids.

♦Caution when combined with drugs metabolized through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents, midazolam).

♦Increases in the dose of Jadenu should be considered when concomitantly used with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir).

♦Careful monitoring of glucose levels should be performed when repaglinide is used concomitantly with Jadenu. Interaction with other CYP2C8 substrates like paclitaxel cannot be excluded.

♦Consider monitoring of theophylline concentration and possible theophylline dose reduction. Interaction with other CYP1A2 substrates may be possible.

♦Caution when combined with drugs with ulcerogenic potential (e.g. NSAIDS, corticosteroids, oral bisphosphonates) or with anticoagulants.

♦Caution should be exercised when deferasirox is combined with busulfan and the patient's plasma concentrations of busulfan should be monitored.

Adverse reactions:

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

♦**Very common**: blood creatinine increased.

♦**Common**: nausea, vomiting, diarrhoea, abdominal pain, abdominal distension, constipation, dyspepsia, rash, pruritus, transaminases increased, proteinuria, headache.

♦**Uncommon**: anxiety, sleep disorder, dizziness, cataracts, maculopathy, deafness, laryngeal pain, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder (Fanconi syndrome), pyrexia, oedema, fatigue.

♦**Rare**: optic neuritis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, oesophagitis.

♦**Adverse drug reactions from post-marketing (frequency unknown)**: renal tubular necrosis, gastrointestinal perforation, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, hepatic failure, hypersensitivity vasculitis, urticaria, alopecia, hypersensitivity reaction (including anaphylactic reaction and angioedema), aggravated anaemia and cytopenia (relationship with Jadenu uncertain).

Packs and prices: Country specific

Legal classification: Country specific

BSS version number: Version 3.3-e

Leaflet revision date: 19-Ju-2018

EXJADE®

Important note: Before prescribing, consult full prescribing information.

Presentation:

Exjade® dispersible tablets

Dispersible tablets containing 125 mg, 250 mg or 500 mg of deferasirox.

Indications: Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over).

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

Dosage: Transfusional iron overload

It is recommended that therapy with Exjade 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.

10 mg per kilogram body weight for pediatric patients not receiving regular blood transfusions

♦Starting daily dose:

Exjade dispersible tablets

The recommended initial daily dose of Exjade is 20 mg/kg body weight.

An initial daily dose of 30 mg/kg may be considered for patients 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 that is numerically half that of the deferoxamine dose could be considered as shown in tables

1 and 3 (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).

♦Monthly monitoring of serum ferritin for assessing patient's response to therapy.

♦Dose adjustment:

It is recommended that serum ferritin be monitored every month and that the dose of Exjade is 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 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients whose serum ferritin level has reached the target (usually between 500 and

1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below

500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of Exjade may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section WARNINGS AND PRECAUTIONS).

♦Maximum daily dose:

Exjade dispersible tablets

The maximum daily dose of dispersible tablets is 40 mg/kg body weight.

Dosage: Non-transfusion-dependent thalassemia syndromes and iron overload

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.

♦Starting daily dose:

Exjade dispersible tablets

The recommended initial daily dose of Exjade is 10 mg/kg body weight.

♦Dose adjustment:

It is recommended that serum ferritin be monitored every month. Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 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 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 is recommended 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.

♦Maximum daily dose:

Exjade dispersible tablets

The maximum daily dose of dispersible tablets is 20 mg/kg body weight.

Administration:

Exjade dispersible tablets

Exjade 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 re-suspended 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.

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 haematological 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.

Women of child-bearing potential, pregnancy, breast-feeding and fertility: ♦Pregnancy: No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. As a precaution, it is recommended that Exjade not be used during pregnancy unless clearly necessary. **♦Breast-feeding:** In animal studies, deferasirox was found to be rapidly and extensively secreted into maternal milk. No effects on the offspring were noted at maternally non-toxic doses of deferasirox. It is not known if deferasirox is secreted into human milk. Breast-feeding while taking Exjade is not recommended. **♦Fertility:** EXJADE did not affect fertility or reproduction in rat studies even at toxic doses.

Warnings/Precautions: The decision to remove accumulated iron should be individualized based on anticipate clinical benefit and risks of chelation therapy. 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 Exjade, usually within the normal range. This has been observed in both pediatric and adult patients with iron overload during the first year of treatment. A study which assessed the renal function of patients enrolled in the registration studies up to 13 years later, confirmed the nonprogressive nature of these serum creatinine observations.

Cases of acute renal failure have been reported following the post-marketing use of Exjade. 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 Exjade. The majority of these patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 microgram/L.

Tests for proteinuria should be performed monthly.

Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting. For adult patients, the daily 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 pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section. 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. If there is a progressive increase in serum creatinine beyond the upper limit of normal, Exjade should be interrupted. Therapy with Exjade may be reinitiated depending on the individual clinical circumstances.

Hepatic impairment

Exjade is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Exjade 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.

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 post-marketing reports of hepatic failure in patients treated with Exjade. Most reports of hepatic failure involved patients with significant co-morbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients. 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 should be interrupted. Once the cause of the liver function test abnormalities has been clarified orafter return to normal levels, cautious re-initiation of Exjade treatment at a lower dose followed by gradual dose escalation may be considered.

Blood disorders

There have been post-marketing reports (both spontaneous and from clinical trials) of

cytopenias in patients treated with Exjade. Most of these patients had pre-existing hematologic disorders that are frequently 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 hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with Exjade should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with Exjade may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal disorders

Gastrointestinal irritation may occur during Exjade treatment. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Exjade. There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients.

Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Exjade 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 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 x 109/L.

Hypersensitivity reactions

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

Skin disorders

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported during the post-marketing period. The risk of other skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If severe skin reactions are suspected Exjade should be discontinued immediately and should not be reintroduced.

Rare cases of erythema multiforme have been reported during Exjade treatment.

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. For more severe rash, where interruption of treatment may be necessary, Exjade may be re-introduced 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

Exjade treatment. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Exjade 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 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.

Exjade has not been associated with growth retardation in children followed for up to 5 years in clinical trials. 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.

Driving and using machines

No studies on the effects of Exjade 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 machines.

Interactions:

Agents that may decrease Exjade systemic exposure

In a healthy volunteer study, the concomitant administration of Exjade (single dose of

30 mg/kg) 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% to 51%). Therefore, the concomitant use of Exjade with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade efficacy. If Exjade and a potent UGT inducer are used concomitantly, increases in the dose of Exjade should be considered based on clinical response to therapy.

Interaction with food

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

Interaction with midazolam and other agents metabolized by CYP3A4

In a healthy volunteer study, the concomitant administration of Exjade and midazolam (a

CYP3A4 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 withsubstances metabolized 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 Exjade (repeated dose of

30 mg/kg/day) and the CYP2C8 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. When Exjade and repaglinide are used concomitantly, careful monitoring of glucose levels should be performed. An interaction between Exjade 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 Exjade (repeated dose of

30 mg/kg/day) 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 Cmax was not affected, but an increase of theophylline Cmax is expected to occur with chronic dosing. When

Exjade and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between

Exjade and other CYP1A2 substrates may be possible.

Other Information

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

The concomitant administration of Exjade and vitamin C has not been formally studied.

Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences.

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

Concomitant administration of Exjade with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of Exjade in patients receiving anticoagulants may increase the risk of gastrointestinal irritation.

EXJADE must not be taken with other iron chelators.

Adverse reactions: ♦*Very common*: blood creatinine increased. **♦*Common***: nausea, vomiting, diarrhea, abdominal pain, abdominal distension, constipation, dyspepsia, rash, pruritus, transaminases increased, proteinuria, headache. **♦*Uncommon***: anxiety, sleep disorder, dizziness, cataracts, maculopathy, deafness, laryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, acute pancreatitis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder(Fanconi syndrome), pyrexia, edema, fatigue. **♦*Rare***: optic neuritis, erythema multiforme, esophagitis. **♦*Adverse drug reactions from post-marketing (frequency unknown)***: renal tubular necrosis, , Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, hepatic failure, hypersensitivity vasculitis, urticaria, alopecia, hypersensitivity reaction (including anaphylactic reaction and angioedema).

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