NOVARTIS

Jadenu®

Iron chelating agent.

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Film-coated tablets.

Active substance

Each film-coated tablet contains 90 mg / 360 mg deferasirox as active substance.

Certain dosage strengths may not be available in all countries.

Excipients

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 carmine aluminum lake (E132).

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

Jadenu 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

Dosage

It is recommended that therapy with Jadenu 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.

Jadenu 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 Jadenu, the dose of Jadenu 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 Jadenu 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 Jadenu that is numerically one third of the deferoxamine dose could be considered as shown in Table 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 14 mg/kg/day of Jadenu).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of Jadenu 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 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 Jadenu 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	**Jadenu 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 microgram/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 microgram/L
	5-10 mg/kg/day Up to 40 mg/kg/day	3.5 - 7 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 microgram/L
Maximum dose	40 mg/kg/day	28 mg/kg/day			
Consider dose interruption					<500 microgram/L

* Packed Red Blood Cells

** Dose conversion explained in more detail in the Table 3

Non-transfusion-dependent thalassemia (NTDT) syndromes

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 overchelation.

Jadenu 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 Jadenu, the dose of Jadenu should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet.

Starting dose

The recommended initial daily dose of Jadenu 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 section 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	Jadenu 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 microgram/L
Adjustment steps	Increase		≥7 mg Fe/g dw	or	>2,000 microgram/L

(every 3-6 months)	5-10 mg/kg/day	3.5 - 7 mg/kg/day	<7 mg Fe/g dw	or	≤2,000 microgram/L
	Decrease				
	5-10 mg/kg/day	3.5 - 7 mg/kg/day			
Maximum dose	20 mg/kg/day	14 mg/kg/day			
	10 mg/kg/day	7 mg/kg/day	Not assessed	and	≤2,000 microgram/L
Dose Interruption			<3 mg Fe/g dw	or	<300 microgram/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 Exjade dispersible tablet and Jadenu film-coated tablet, as well as deferoxamine is shown in Table 3

Table 3 Dose conversion

Deferoxamine dose**	Daily dose of Exjade Dispersible tablets	Daily dose for Jadenu Film-coated tablets
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

Jadenu has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Jadenu treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range. 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 approximately 50%. Jadenu 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

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 (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Creatinine clearance <60 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. 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 non-progressive nature of these serum creatinine observations.

Cases of acute renal failure have been reported following the post-marketing use of deferasirox (see section ADVERSE DRUG REACTIONS). Although causal relationship with deferasirox 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.

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.

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 diarrhea or vomiting.

For adult patients, the daily dose of Jadenu 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 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, Jadenu should be interrupted. Therapy with Jadenu may be reinitiated depending on the individual clinical circumstances.

The recommendations for renal function monitoring are summarized in the Table 4.

Table 4 Recommendations for renal function monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and/or	Twice (2x)
Contraindicated	>2 times age-appropriate ULN*	or	<60 mL/min
Monitoring	**Monthly**	**and/or**	**Monthly**
	For patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress the renal function as they may be more at risk of complications in the first month after initiation, or modification of therapy (including switching formulation), monitoring should be:		
	Weekly	**and/or**	**Weekly**
Reduction of daily dose by 7 mg/kg/day if following renal parameters are observed on two consecutive visits and cannot be attributed to other causes:			
Adult patients	>33% above pre-treatment average (non-progressive rise)		
Pediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and pediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic Impairment

Jadenu is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see sections 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 post-marketing reports of hepatic failure in patients treated with deferasirox. 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 (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, Jadenu 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 Jadenu 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 deferasirox. Most of these patients had pre-existing hematologic 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 hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with Jadenu should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with Jadenu may be considered, once the cause of the cytopenia has been elucidated.

Gastrointestinal Disorders

Gastrointestinal irritation may occur during Jadenu treatment. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. 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 (see section ADVERSE DRUG REACTIONS). Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Jadenu 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 Jadenu 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, Jadenu should be discontinued and appropriate medical intervention instituted. Jadenu 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 (SCARs), 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 Jadenu should be discontinued immediately and should not be reintroduced.

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

Skin rashes may appear during Jadenu treatment. For rashes of mild to moderate severity, Jadenu may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Jadenu 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 deferasirox treatment (see section ADVERSE DRUG REACTIONS). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Jadenu 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 Jadenu 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, height and sexual development in pediatric patients should be monitored at regular intervals (every 12 months).

Driving and using machines

No studies on the effects of Jadenu 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.

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, diarrhea, 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 post-marketing reports of hepatic failure in patients treated with deferasirox. 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.

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 (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 deferasirox. 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 5, 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 5 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:	Glycosuria, renal tubular disorder (Fanconi 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

Spontaneously reported adverse reactions, presented in Table 6, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 6 Adverse drug reactions derived from spontaneous reports (frequency not known)

Immune system disorders
hypersensitivity reaction (including anaphylactic reaction and angioedema)
Gastrointestinal disorders
gastrointestinal perforation
Hepatobiliary disorders
hepatic failure
Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
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

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 pre-existing hematologic disorders that are frequently associated with bone marrow failure (see Section WARNINGS AND PRECAUTIONS). 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 Jadenu 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% to 51%). Therefore, the concomitant use of Jadenu with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Jadenu efficacy. If Jadenu and a potent UGT inducer are used concomitantly, increases in the dose of Jadenu should be considered based on clinical response to therapy.

Interaction with food

The C_{max} of deferasirox film-coated tablets was moderately increased (by 29%) when taken with a high-fat meal. Jadenu may be taken either on an empty stomach or with a light meal (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 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 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 deferasirox (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP2C8 substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide AUC and C_{max} by 131% (90% CI: 103% to 164%) and 62% (90% CI: 42% to 84%), respectively. When 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 aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, deferasirox must not be taken with aluminum-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 Animal data). The potential risk for humans is unknown.

As a precaution, it is recommended that Jadenu not be used during pregnancy unless clearly necessary.

Data

Animal data

The potential for toxicity to reproduction was assessed in rats and rabbits.

Those studies showed that 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 Jadenu 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.

OVERDOSAGE

Single doses up to 40 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 28 mg/kg Jadenu) 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 erroneously 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

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, and does not cause constant low serum levels of these metals.

Pharmacodynamics (PD)

In an iron balance metabolic study in iron overloaded adult thalassemic 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 anemia 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 microgram /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 deferasirox 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.

In patients with non-transfusion-dependent thalassemia syndromes and iron overload, treatment with deferasirox at a dose of 10 mg/kg/day (dispersible tablet formulation) for one year led to a reduction in mean liver iron concentration from baseline by -3.80 mg Fe/g dw, while an increase of 0.38 mg Fe/g dw was observed in patients treated with placebo. In addition,

treatment with deferasirox at a dose of 10 mg/kg/day for one year led to a reduction in mean serum ferritin from baseline by -222.0 microgram/L, while an increase of 114.5 microgram/L was observed in patients treated with placebo.

Pharmacokinetics (PK)

Jadenu 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 dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions . The C_{max} was increased by 30% (90% CI: 20.3% to 40.0%); however a clinical exposure/response analysis has revealed no evidence of clinically relevant effects of such an increase.

Absorption

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (T_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) 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 Jadenu 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 Jadenu 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 feces (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 has not been studied in elderly patients (aged 65 or older).

Renal or hepatic impairment

The pharmacokinetics of deferasirox has not been studied in patients with renal impairment.

The average AUC of deferasirox in 6 subjects with mild hepatic impairment (Child-Pugh A) increased 16% over that found in 6 subjects with normal hepatic function, while the average AUC of deferasirox in 6 subjects with moderate hepatic impairment (Child-Pugh B) increased 76% over that found in 6 subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment increased 22% over that found in subjects with normal hepatic function. The impact of severe hepatic impairment (Child-Pugh C) was assessed in only one subject (see section DOSAGE AND ADMINISTRATION and section WARNINGS AND PRECAUTIONS). The pharmacokinetics of deferasirox was not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

CLINICAL STUDIES

Clinical efficacy studies were conducted with deferasirox dispersible tablets. 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 7). 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 7).

Table 7 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	Deferoxamine	Deferasirox	Deferoxamine	Deferasirox Mean ± SD (n)	Deferoxamine Mean ± SD (n)	Deferasirox Mean ± SD (n)	Deferoxamine 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 tablets 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 tablets 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 primary endpoint is 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). Changes in the serum ferritin was a secondary endpoint in the study. The results of this study suggest that there is a positive impact of deferasirox on serum ferritin levels. 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 tablets. 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 8). 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 tablets 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 9).

Table 8 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 9 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)

A randomized, double-blind, placebo-controlled study to compare deferasirox dispersible tablets and placebo was conducted in patients with non-transfusion-dependent thalassemia syndromes and iron overload. Patient's ≥10 years of age were enrolled in the study in a 2:1:2:1 randomization to receive deferasirox dispersible tablets 5 mg/kg/day, or 10 mg/kg/day, or matching placebo.

Transfusion independency of the patients was confirmed by the fact that blood transfusions 6 months prior to study start were not allowed and patients were excluded if a regular transfusion program was anticipated during the study. Iron overload was diagnosed by a serum ferritin >300 microgram/L at screening (two consecutive values at least 14 days apart from each other) and LIC ≥5 mg Fe/g dw measured by R2 MRI at screening. All patients with non-transfusion-dependent thalassemia syndromes were allowed with the exception of patients with HbS-variants or those whose clinical condition allowed phlebotomy.

In total, 166 patients were randomized. Demographics were well balanced. The main underlying disease was beta-thalassemia intermedia in 95 (57.2%) patients and HbE beta-thalassemia in 49 (29.5%) patients. The primary efficacy endpoint of change in liver iron concentration (LIC) from baseline to Week 52 was statistically significant in favor of both deferasirox treatment groups compared with placebo (Table 10). Furthermore, a statistically significant dose effect of deferasirox was observed in favor of the 10 mg/kg/day dispersible tablet dose.

Table 10 Primary efficacy analysis – Analysis of covariance of absolute change in liver iron concentration (mg Fe/g dw) between baseline and week 52 (Full Analysis Set)

	Deferasirox disp. tablets 5 mg/kg/day (N=55)	**Deferasirox disp. tablets** 10 mg/kg/day (N=55)	Placebo (N=56)
Change from baseline			
Number of evaluable patients	51	54	54
Least squares mean	-1.95	-3.80	0.38
Standard error	0.500	0.484	0.486
95% confidence interval	-2.94, -0.96	-4.76, -2.85	-0.59, 1.34
Difference of deferasirox - Placebo			
Least squares mean	-2.33	-4.18	-
Standard error	0.700	0.687	-
95% confidence interval (1)	-3.89, -0.76	-5.71, -2.64	-
p-value (2)	0.001	<.001	-
Difference of deferasirox 10 mg/kg - deferasirox 5 mg/kg			
Least squares mean	-	-1.85	-
Standard error	-	0.695	-
95% confidence interval	-	-3.22, -0.48	-
p-value (3)	-	0.009	-

Estimates were obtained from an ANCOVA model for change in LIC between baseline and Week 52 with treatment as factor and baseline LIC as covariate.

(1) two-sided simultaneous confidence intervals using Dunnett's adjustment

(2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in LIC is not greater under deferasirox disperible tablets than under placebo. Critical alpha-level: 0.025

(3) two-sided p-value testing the hypothesis that the change in LIC is identical in the two deferasirox groups. Critical alpha-level: 0.05

The last available post-baseline LIC was carried forward if no LIC value was available at Week 52.

Only patients with both baseline and at least one post-baseline LIC value were included for this analysis.

The primary efficacy result was supported by additional analyses which showed a clear dose-response effect; this was reflected by a greater percentage of patients with an LIC decrease of ≥3 mg Fe/g dw in the 10 mg/kg/day deferasirox dispersible tablet group compared to the 5 mg/kg/day group (56.4% versus 32.7%, respectively). In addition, a reduction of ≥30% in LIC between baseline and Week 52 was reported in approximately twice as many patients in the 10 mg/kg/day deferasirox dispersible tablet group (49.15%) compared to the 5 mg/kg/day group (25.5%).

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.

Tests of genotoxicity in vitro were either negative (Ames test, chromosomal aberration test) or positive (V79 screen). Deferasirox caused formation of micronuclei in vivo in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Jadenu should not be used after the date marked “EXP” on the pack.

Information might differ in some countries.

INSTRUCTIONS FOR USE AND HANDLING

Note: Jadenu must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

Presentation:

For both 90 mg and 360 mg strengths: Tablets are packed in PVC/PVDC blister pack with alu foil, in a box of 30 or 90 tablets.

Not all presentations may be available locally.

International Package Leaflet

Information issued: Jul 2019.SINv1

® = registered trademark

Novartis Pharma AG, Basel, Switzerland