NOVARTIS

JADENU

(deferasirox)

180 and 360 mg film-coated tablets

Professional Information

Document status: Final

Approval date: 31 March 2026

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

JADENU 180 mg film-coated tablets

JADENU 360 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JADENU 180 mg film-coated tablet contains 180 mg deferasirox

JADENU 360 mg film-coated tablet contains 360 mg deferasirox

Sugar free

3. PHARMACEUTICAL FORM

JADENU® 180 mg: Medium blue, ovaloid, biconvex film-coated tablet with bevelled edges, "NVR" imprinted on one side and "180" on a slight upward slope in between two debossed curved lines on the other side.

JADENU® 360 mg: Dark blue, ovaloid, biconvex film-coated tablet with bevelled edges, "NVR" imprinted on one side and "360" on a slight upward slope in between two debossed curved lines on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

JADENU is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adult and paediatric patients (aged 2 years and over).

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

JADENU 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).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

JADENU 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.

Transfusional iron overload

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.

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 individualised 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 dispersible tablet formulation.

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 Tables 4.1 (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 minimise the risk of overchelation (see section 4.4). If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. 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 4.4).

The corresponding recommended doses for both formulations are shown in Table 4-1.

Table 4-1 Transfusional iron overload: Recommended doses

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

Consider dose interruption				<500 microgram/ L

* Packed Red Blood Cells

** Dose conversion explained in more detail in the Table 4.3

Non-transfusion-dependent thalassaemia syndromes

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

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 minimise the risk of overchelation (see section 4.4). 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 medicine well**.** Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤2,000 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.

Table 4-2 Table illustrating Non-Transfusion-Dependent Thalassaemia (NTDT): Recommended doses

	Jadenu Film-coated tablets/granules	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	7 mg/kg/day	≥5 mg Fe/g dw	or	>800 microgram/L
Adjustment steps (every 3 to 6 months)	Increase	≥7 mg Fe/g dw	or	>2,000 microgram/L
	3.5 to 7 mg/kg/day			
	Decrease	<7 mg Fe/g dw	or	≤2,000 microgram/L
	3.5 to 7 mg/kg/day			
Maximum dose	14 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 thalassaemia syndromes

Information on dose conversion between JADENU film-coated tablets, as well as deferoxamine is shown in Table 4-3 below.

Table 4-3 Dose conversion

Deferoxamine dose**	**Daily dose for Jadenu Film-coated tablets**
10 mg/kg	3.5 mg/kg
20 mg/kg	7 mg/kg
30 mg/kg	10.5 mg/kg
40 mg/kg	14 mg/kg
50 mg/kg	17.5 mg/kg
60 mg/kg	21 mg/kg
Not applicable*	24.5 mg/kg
Not applicable*	28 mg/kg

* Not recommended in deferoxamine label

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

Patients with renal impairment

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

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 4.3). 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 4.4).

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 elderly patients should be monitored closely for adverse reactions that may require a dose adjustment.

Paediatric patients

The dosing recommendations for paediatric 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 minimise the risk of overchelation (see section 4.4). Changes in weight of paediatric patients over time must be taken into account when calculating the dose.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Creatinine clearance < 40 mL/min
- Repaglinide (see section 4.5)
- High risk myelodysplastic syndrome (MDS) patients and patients with other haematological and nonhaematological malignancies with limited expected survival (< 1 year) who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

- Severe hepatic impairment (Child-Pugh C)
- Pregnancy and breastfeeding (see section 4.6)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant administration of JADENU with medicines that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of JADENU in patients receiving anticoagulants may increase the risk of gastrointestinal complications such as ulceration and haemorrhage.

There have been post marketing reports of hepatic failure in patients treated with JADENU. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

The decision to remove accumulated iron should be individualised based on anticipated clinical benefit and risks of chelation therapy.

Caution should be used in elderly patients due to a higher frequency of adverse reactions.

Body weight and longitudinal growth in paediatric patients should be monitored at regular intervals (every 12 months).

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 4.2).

Renal

Non-progressive rises in serum creatinine have been noted in patients treated with JADENU, usually within the normal range. This has been observed in both paediatric 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 JADENU. (see section 4.8). Although causal relationship with JADENU 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 other medicinal products that may depress renal function may be more at risk of complications and 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. JADENU should not be used in patients with creatinine clearance less than 40 mL/min (see section 4.3).

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

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

Tests for proteinuria should be performed monthly. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting.

For adult patients, the daily dose of 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 4.2). For paediatric 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.

Table 4-4 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	<40 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 (Jadenu film-coated tablets) 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)		
Paediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and paediatric patients	Progressive increase in serum creatinine		

	beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic

JADENU is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3). Deferasirox is principally eliminated by glucuronidation and is minimally (about 8 %) metabolised 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 JADENU. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

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.

Gastrointestinal

Gastrointestinal irritation may occur during JADENU treatment. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving JADENU. There

have been rare reports of fatal GI haemorrhage, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients. Medical practitioners and patients should remain alert for signs and symptoms of GI ulceration and haemorrhage 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 medicines that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts <50 x 10^9/L.

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.

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 reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction may be conducted in combination with a short period of oral steroid administration. Cases of erythema multiforme have been reported during JADENU treatment.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving JADENU, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 4.8). 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.

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with JADENU treatment (see section 4.8). 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.

Blood disorders

There have been post marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with JADENU. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see section 4.8). The relationship of these episodes to treatment with JADENU is uncertain. In line with the standard clinical management of such haematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with JADENU should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with JADENU may be considered, once the cause of the cytopenia has been elucidated.

Other considerations

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 4.2).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Concomitant administration of JADENU with medicines that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of JADENU in patients receiving anticoagulants may increase the risk of gastrointestinal complications such as ulceration and haemorrhage.

Interaction with midazolam and other medicines metabolised by CYP3A4

In a healthy volunteer study, the concomitant administration of JADENU and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17 % (90 % CI: 8 % - 26 %). In the clinical setting, this effect may be more pronounced.

Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive medicines).

Medicines that may decrease JADENU systemic exposure

In a healthy volunteer study, the concomitant administration of JADENU (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 % - 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 repaglinide and other medicines metabolised by CYP2C8

In a healthy volunteer study, the concomitant administration of JADENU (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 C_{max} by 131 % (90 % CI: 103 % - 164 %) and 62 % (90 % CI: 42 % - 84 %), respectively. An interaction between JADENU and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other medicines metabolised by CYP1A2

In a healthy volunteer study, the concomitant administration of JADENU (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 C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing.

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

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.

Other information

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

The concomitant administration of JADENU and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/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 in patients with severe iron overload, and in whom monotherapy has not been able to control their iron load) was consistent with that characterised for monotherapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Safety in pregnancy and lactation has not been established. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown.

JADENU should not be used during pregnancy. (see section 4.3)

Breastfeeding

In animal studies, JADENU was found to be rapidly and extensively secreted into maternal milk. No effect on the offspring was noted. It is not known if JADENU is secreted into human milk. Breastfeeding while taking JADENU is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of JADENU on the ability to drive and use machines have been performed. Patients experiencing dizziness should exercise caution when driving or operating machinery (see section 4.8).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

In clinical trials in patients with transfusional iron overload, the most frequent reactions reported during chronic treatment with JADENU in adult and paediatric patients include gastrointestinal disturbances in about 26 % of patients (mainly nausea, vomiting, diarrhoea, or abdominal pain), and skin rash in about 7 % of patients.

These reactions are dose-dependent. 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 4.4).

In clinical trials 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 JADENU. 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 JADENU. Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

In a 1-year, randomised, double-blind, placebo-controlled study in patients with non-transfusion-dependent thalassaemia syndromes and iron overload, diarrhoea (9,1 %), rash (9,1 %), and nausea (7,3 %) were the most frequent study medicine-related adverse events reported by patients receiving 10 mg/kg/day of JADENU. Abnormal serum creatinine and creatinine clearance values were reported in 5,5 % and 1,8 %, respectively, of

patients receiving 10 mg/kg/day of JADENU. 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 of JADENU. High-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with JADENU (see section 4.4).

The following adverse reactions, listed in Table 1, have been reported in clinical studies following treatment with JADENU. Adverse reactions are ranked below using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (> 1/10 000, < 1/1000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1– 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:	gastritis, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers, duodenal ulcer, acute pancreatitis
	Rare	oesophagitis
Hepatobiliary disorders		
	Common:	Increased transaminases
	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:	Increased blood creatinine
	Common:	proteinuria
	Uncommon	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 paediatric patients with transfusion-dependent thalassaemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed.

Post marketing side effects

Spontaneously reported post marketing adverse reactions, presented in Table 2, are reported voluntarily and it is not possible to reliably establish frequency or a causal relationship to medicine exposure.

Table 2– Adverse drug reactions derived from post marketing experience

Renal and urinary disorders: Acute renal failure (mostly serum creatinine increases > 2 x upper limit of normal, and usually reversible after treatment interruption) (see section 4.4) tubulointerstitial nephritis
Blood and lymphatic system disorder: Anaemia **Hepatobiliary disorders:** Hepatic failure
Skin and subcutaneous disorders: Stevens-Johnson syndrome**,** hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
Immune system disorders:

Hypersensitivity reaction (including anaphylactic reaction and angioedema)

There have been post marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia and thrombocytopenia in patients treated with JADENU. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see section 4.4). The relationship of these episodes to treatment with JADENU is uncertain (see section 4.4).

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 anaemia in patients treated with deferasirox. Most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see section 4.4). 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.

Paediatric population

Renal tubulopathy has been reported in patients treated with JADENU. The majority of these patients were children and adolescents with beta-thalassaemia 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 haemosiderosis 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 diarrhoea (1,9 %). Overall growth and development were not affected in this paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 OVERDOSE

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 sign of acute overdose are digestive effects such as abdominal pain, diarrhoea, 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 with resolved after treatment. There is no specific antidote for deferasirox.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC03

5.1 PHARMACODYNAMIC PROPERTIES

Deferasirox is an orally active chelator that is selective for iron (III).

It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

5.2 PHARMACOKINETICS

JADENU film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the dispersible tablet formulation. After strength-adjustment, the film-coated tablet formulation (360 mg strength) was equivalent to the 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 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 from deferasirox dispersible tablets is 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 the 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/metabolism

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

Elimination:

Deferasirox and its metabolites are primarily excreted in the faeces (84 % of the dose). Renal excretion of deferasirox and its metabolites is minimal (8 % of the dose). The mean elimination half-life (T1/2) 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:

Paediatric patients

The overall exposure of adolescents (12 to ≤ 17 years) and children (2 to <12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was

about 50 % lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Gender

Females have a moderately lower apparent clearance (by 17,5 %) for deferasirox compared to males. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Elderly patients

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

Renal or hepatic impairment

In a single dose study, 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. Deferasirox should not be used in patient with severe hepatic impairment (Child-Pugh C). The pharmacokinetics of deferasirox have not been studied in patients with renal impairment.

6. LIST OF PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS:

Microcrystalline cellulose, crospovidone, povidone K30, magnesium stearate, colloidal silicon dioxide, poloxamer 188.

Excipients of film-coating: Hypromellose, titanium dioxide (E 171), polyethylene glycol 4000, talc, FD&C blue #2/Indigo carminine aluminium lake (E132).

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C in the original package. Protect from moisture.

6.5 NATURE AND CONTENTS OF THE CONTAINER:

30 film-coated tablets in blisters composed of a colourless, transparent laminated plastic film made of PVC/PVDC film with an aluminium foil backing, or a PA/AL/PVC (polyamide /aluminium /polyvinylchloride) film with an aluminium foil backing.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

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8. REGISTRATION NUMBERS:

JADENU® 180mg: 50/27/0769

JADENU® 360 mg: 50/27/0770

9. DATE OF FIRST AUTHORISATION:

21 January 2021

10. DATE OF REVISION OF TEXT

31 March 2026

2015-PSB/GLC-0763-s, 2017-PSB/GLC-0882-s, 2018-PSB/GLC-0934-s, 2019-PSB/GLC-1065-s