Important Information to Remember About Jadenu® (Deferasirox) Treatment

This guide highlights the main important information about requirements for Jadenu® dosing, dose adjustment and biological monitoring. For complete information about Jadenu® dosing, dose adjustment and biological monitoring, please refer to the latest Singapore package insert for Jadenu®.

Indications[1]

Chronic Transfusional Iron Overload

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).

Non–Transfusion-Dependent Thalassemia

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

Contraindications[1]

- Jadenu is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients
- Jadenu is contraindicated in with creatinine clearance <60 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal.

- Jadenu has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 mL/min

- Jadenu is contraindicated in 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.

Starting Jadenu® treatment

Before initiating therapy

Pretreatment Measures[1]	
Test	**Pretreatment**
SF	✓
LIC[a]	✓
Serum creatinine and/or CrCl	2×
Proteinuria	✓
Serum transaminases (ALT and AST)	✓
Bilirubin	✓
Alkaline phosphatase	✓
Auditory testing	✓
Ophthalmic testing	✓
Body weight, height, and sexual development (pediatric patients)	✓

ALT: alanine aminotransferase; **AST:** aspatate aminotransferase; **CrCl:** creatinine clearance; **LIC:** liver iron concentration; **SF:** serum ferritin.

[a]For non–transfusion-dependent thalassemia (NTDT) patients: Measure iron overload with LIC. For patients with NTDT, LIC is the preferred method of iron overload determination and should be used wherever available. In patient with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of overchelation.[1]

Jadenu® film-coated tablets dosing for patients with chronic transfusional iron overload

- Recommended initial dose: 14 mg/kg/day body weight[1]
- Doses >28 mg/kg/day are not recommended[1]
- Monitor your patients regularly[1]

Jadenu film-coated tablets starting dose and dose adjustment for patients with transfusional iron overload[1]

INITIATE therapy	UP-TITRATE to achieve target when necessary[a]	DOWN-TITRATE to avoid overchelation	INTERRUPTION Consider interruption once target has been achieved
14 mg/kg body weight per day (recommended starting dose) 20 U (~100 ml/kg) PRBCs or SF >1000 µg/l	Increase in increments of 3.5 to 7 mg/kg/day up to a dose of 28 mg/kg/day	Decrease dose in steps of 3.5 to 7 mg/kg/day when SF has reached the target of usually between 500 and 1,000 µg/l	SF consistently <500 µg/l
7 mg/kg body weight per day <7 ml/kg/month of PRBCs (~ <2 units/month for an adult)	Increase in increments of 3.5 to 7 mg/kg/day up to a dose of 28 mg/kg/day		
21 mg/kg body weight per day >14 ml/kg/month of PRBCs (~ >4 units/month for an adult)	Increase in increments of 3.5 to 7 mg/kg/day up to a dose of 28 mg/kg/day Consider alternative treatment options if no satisfactory control is achieved at doses >28 mg/kg/day		
Patients already well managed on treatment with deferoxamine A starting dose of Jadenu film-coated tablets that is numerically one third that of the deferoxamine dose could be considered	Increase in increments of 3.5 to 7 mg/kg/day up to a dose of 28 mg/kg/day		

PRBCs: packed red blood cells; **SF:** serum ferritin; **U:** units.

[a]In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric transfusional iron overload patients[1]

- The dosing recommendations for pediatric patients aged 2 to 17 years are the same as for adult patients. Changes in weight of pediatric patients over time must be taken into account when calculating the dose. 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

Jadenu® film-coated tablets dosing for patients with non–transfusion-dependent thalassemia (NTDT)

- Recommended initial dose: 7 mg/kg/day body weight[1]
- Doses >14 mg/kg/day are not recommended[1]
- Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present[1]
- Monitor your patients regularly[1]

Jadenu film-coated tablets starting dose and dose adjustment for patients with non–transfusion-dependent thalassemia[1]

INITIATE therapy[a]	UP-TITRATE to achieve target when necessary[a,b]	DOWN-TITRATE to avoid overchelation	STOP therapy once target has been achieved
7 mg/kg/day	Increase in increments of 3.5 to 7 mg/kg/day up to a maximum dose of 14 mg/kg/day	Decrease in steps 3.5 to 7 mg/kg/day	Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present
LIC ≥5 mg Fe/g dw OR SF consistently >800 µg/l	**LIC ≥7 mg Fe/g dw OR SF consistently >2000 µg/l**	**LIC <7 mg Fe/g dw OR SF consistently ≤2000 µg/l**	**GOAL LIC <3 mg Fe/g dw OR SF consistently <300 µg/l**

DW: dry weight; **LIC:** liver iron concentration; **SF:** serum ferritin.

[a]Doses above 14 mg/kg/day are not recommended for patients with NTDT. In patients whose LIC was not assessed and SF is ≤2000 µg/l, dosing should not exceed 7 mg/kg/day.

[b]In addition, a dose increase should only be considered if the patient is tolerating the medicinal product well.

Pediatric NTDT patients[1]

- The dosing recommendations for pediatric patients aged 2 to 17 years with transfusional iron overload are the same as for adult patients. Changes in weight of pediatric patients over time must be taken into account when calculating the dose. 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

Considerations for treatment interruption of Jadenu®[1]

Consideration	Treatment interruption conditions
SF	Consistently <500 µg/l (in transfusional iron overload) or <300 µg/l (in NTDT syndromes)
Serum creatinine	Adult and pediatric: progressive increase in serum creatinine beyond the upper limit of normal – also refer patient to renal specialist and consider biopsy
Proteinuria	Persistent abnormality–also refer patient to renal specialist and consider biopsy
Tubular markers	Abnormalities in levels of tubular markers and/or if clinically indicated – also refer patient to renal specialist and consider biopsy (also consider dose reduction)
Serum transaminase (ALT and AST)	Persistent and progressive increase in liver enzyme
SJS, TEN, DRESS or any other SCAR:	Discontinue immediately and do not reintroduce
Hypersensitivity reactions	Occurrence of reaction: discontinue and institute appropriate medical intervention. Do not reintroduce in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock
Vision and hearing	Disturbances during the treatment (also consider dose reduction)
Unexplained cytopenia	Development of unexplained cytopenia

SF: serum ferritin; **SJS:** Stevens-Johnson syndrome; **TEN:** toxic epidermal necrolysis; **DRESS:** drug reaction with eosinophilia and systemic symptoms; **SCAR:** severe cutaneous adverse reaction.

Monitoring recommendations for patients prior to and during Jadenu® treatment[1]

	Baseline	In the first month after initiation of Jadenu®	Monthly	Every 3 months	Yearly
SF	✓		✓		
LIC[a]	✓			✓	
Serum creatinine and/or creatinine clearance (CrCl)	2×	Weekly*	✓		
Proteinuria	✓		✓		
Serum transaminases, bilirubin, alkaline phosphatase	✓	Every 2 weeks	✓		
Body weight, height, and sexual development (pediatric patients)	✓				✓
Auditory/ophthalmic testing (including funduscopy)	✓				✓

[a]For non–transfusion-dependent thalassemia (NTDT) patients: Measure iron overload with LIC. For patients with NTDT, LIC is the preferred method of iron overload determination and should be used wherever available. In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of overchelation.[1]

*In patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function, 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.

There have been 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. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly.

The results of the tests for serum creatinine, CrCl, proteinuria, SF, liver transaminases, bilirubin, and alkaline phosphatase should be recorded and regularly assessed for trends. The results should also be noted in the patient's medical records, along with pretreatment baseline levels for all tests.

Summarized checklist for Jadenu® dosing and biological monitoring

Chronic transfusional iron overload

After ~100 ml/kg of packed red blood cells (~20 units) or serum ferritin levels >1,000 µg/l
→ Starting dose: 14 mg/kg/day*

Non-transfusion dependent thalassemia

If LIC ≥5 mg Fe/g dw or serum ferritin consistently >800 µg/l
→ Starting dose: 7 mg/kg/day*

Start treatment

Biological monitoring

Serum ferritin:
- At baseline
- Routine monthly monitoring

LIC (NTDT patients only):
- At baseline
- Every 3 months

Serum creatinine and/or creatinine clearance:
- At baseline in duplicate assessments
- Weekly, in the first month after initiation of Jadenu or after dose modification[a]
- Routine monthly monitoring

Proteinuria:
- At baseline
- Routine monthly monitoring

Hepatic function (serum transaminases, bilirubin, alkaline phosphatase):
- At baseline
- Every 2 weeks in the first month after initiation of Jadenu
- Routine monthly monitoring

Body weight, height and sexual development (pediatric patients):
- At baseline
- Routine yearly monitoring

Auditory/opthalmic testing (including funduscopy):
- At baseline
- Routine yearly monitoring

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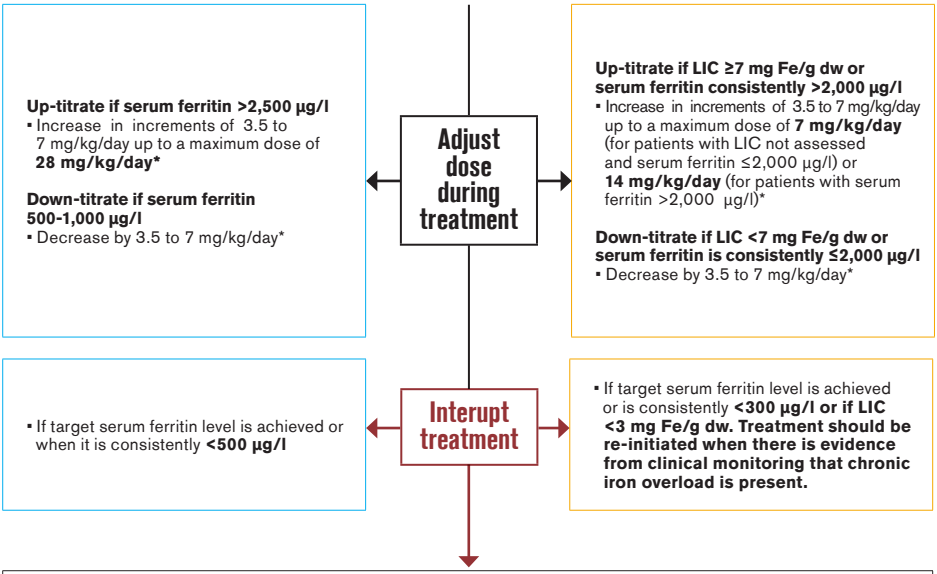

LIC: liver iron concentration; **NTDT:** Non-Transfusion Dependent Thalassemia

*Further examples of dose calculation or adjustments are provided in the label.

[a] Weekly monitoring is not for all patients: 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.

§ Refer to the product label for other dose adjustments/interruptions for renal and hepatic abnormalities, metabolic acidosis, SCARs, hypersensitivity reactions.

Renal safety profile

Jadenu has not been studied in patients with renal impairment and is contraindicated in patients with estimated CrCl <60 ml/min or serum creatinine >2 times the age-appropriate upper limit of normal.

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

Non-progressive rises in serum creatinine have been noted in patients treated with Jadenu usually within the normal range.

- Postmarketing cases of acute renal failure have been reported.
- Although causal relationship could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

Monitoring serum creatinine and CrCl[1]

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, CrCl** (estimated with the Cockcroft-Gault or Modification of Diet in Renal Disease formula in adults and with the Schwartz formula in children), **should be monitored prior to therapy, weekly in the first month after initiation* or modification of therapy with Jadenu, and monthly thereafter.**

* In patients with pre-existing renal conditions, or patients who are receiving medicinal products that may depress renal function.

Methods for estimating CrCl

For your reference, here is a brief overview of methods to estimate CrCl in adults and children when prescribing Jadenu.

Adult

Once a method has been selected, you should not interchange between formulas.

Cockcroft–Gault formula[2]

The Cockcroft-Gault formula employs serum creatinine measurements and the patient's weight to predict CrCl.

The formula states CrCl in ml/min.

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72^{a} \times \text{serum creatinine (mg/100 ml)}}$$

In female patients, creatinine clearance is multiplied by 0.85.

CKD-EPI equation[3,4]

A general practice and public health perspective favors adoption of the CKD-EPI equation in North America, Europe, and Australia and using it as a comparator for new equations in all locations.

Glomerular filtration rate (GFR) = $141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Pediatric

Schwartz formula[5]

$$\text{Creatinine clearance (ml/min)} = \frac{\text{constant}^{b} \times \text{height (cm)}}{\text{serum creatinine (mg/dl)}}$$

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

[a]If serum creatinine is provided in mmol/l instead of mg/dl, the constant should be 815 instead of 72.

[b]The constant is 0.55 in children and adolescent girls, or 0.70 in adolescent boys.

Renal safety profile (continued)

Renal monitoring and actions[1]

Jadenu® (deferasirox) film-coated tablets: Reduce the dose by 7 mg/kg/day, if[1]

- Adult: Non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits
- Pediatric: Serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits

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Interrupt treatment after dose reduction if progressive increase in serum creatinine is beyond the upper limit of normal.

Monitor **renal tubular function** (eg, proteinuria, glycosuria in patients without diabetes and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)

- Consider dose reduction or interruption if there are abnormalities and/or as clinically indicated
- Renal tubulopathy has been mainly reported in children and adolescents with β-thalassemia and serum ferritin levels <1500 µg/l treated with Jadenu

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Refer patient to a renal specialist and consider **renal biopsy**

- When serum creatinine is significantly elevated and if another abnormality has been detected (eg, proteinuria, signs of Fanconi syndrome) despite dose reduction or interruption

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Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be at greater risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting.

Hepatic safety profile

Liver function assessment

Liver function test elevations have been observed in patients treated with Jadenu

- Postmarketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with Jadenu
- Most reports of hepatic failure involved patients with significant co-morbidities including preexisting liver cirrhosis

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Monitor **serum transaminases, bilirubin and alkaline phosphatase** before the initiation of treatment, every 2 weeks during the first month and monthly thereafter

- Interrupt treatment if persistent and progressive increase in serum transaminase levels is noted

Recommendations in hepatic impairment

Jadenu is not recommended in patients with preexisting severe hepatic disease (Child-Pugh Class C).

In patients with moderate hepatic impairment (Child-Pugh Class B)

- The starting dose should be reduced by approximately 50%
- Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month

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The pharmacokinetics of Jadenu were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

Notes

References: 1. Jadenu (deferasirox) film coated tablets Singapore Package Insert Novartis July 2019. 2. Cockcroft DW, Gault MH. Nephron. 1976;16(1): 31-41. 3. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Ann Intern Med. 2012;156(11):785-795. 4. Levey AS, Stevens LA, Schmid CH, et al; for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Ann Intern Med. 2009;150(9):604-612. 5. Schwartz GJ, Brion LP, Spitzer A. Pediatr Clin North Am. 1987;34(3):571-590.

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