

Regulatory Affairs

**EXJADE<sup>®</sup>** (deferasirox) Dispersible tablets

125 mg, 250 mg, 500 mg Dispersible tablets

(in some countries marketed as ASUNRA<sup>®</sup>

100 mg, 400 mg Dispersible tablets)

**OLEPTISS<sup>®</sup>** (deferasirox) Film-coated tablets and granules

90 mg, 180 mg, 360 mg Film-coated tablets

90 mg, 180 mg, 360 mg Granules

(locally available strengths may differ)

**Summary of Product Characteristics (SmPC)**

**Version 4.0**

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## Table of contents

Table of contents .....	2
List of tables .....	2
1 Trade names.....	4
2 Description and composition.....	4
3 Indication.....	4
4 Dosage and administration .....	5
5 Contraindications.....	12
6 Warnings and precautions .....	13
7 Adverse drug reactions .....	17
8 Interactions .....	20
9 Pregnancy, lactation, females and males of reproductive potential .....	22
9.1 Pregnancy.....	22
9.2 Lactation.....	22
9.3 Females and males of reproductive potential.....	22
10 Overdosage.....	22
11 Clinical pharmacology.....	23
12 Clinical studies .....	27
13 Non-clinical safety data.....	32
14 Pharmaceutical information.....	32

## List of tables

Table 4-1	Transfusional iron overload: Recommended doses .....	8
Table 4-2	NTDT: Recommended doses .....	10
Table 4-3	Dose conversion .....	11
Table 6-1	Recommendations for renal function monitoring .....	14
Table 7-1	Adverse drug reactions reported in clinical studies .....	18
Table 7-2	Adverse drug reactions derived from spontaneous reports (frequency not known) .....	19
Table 12-1	Ratio of iron excretion/iron intake and change in serum ferritin levels from baseline to 1 year of treatment in the primary efficacy study .....	28
Table 12-2	Geometric mean of T2* (ms) at baseline, and at the end of year 1, 2, and 3 .....	30
Table 12-3	Transition table of cardiac T2* from core baseline to end of E2 (year 3) .....	30

Table 12-4	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) .....	31
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## 1 Trade names

EXJADE® 125 mg, 250 mg, 500 mg dispersible tablets.

ASUNRA® 100 mg, 400 mg dispersible tablets.

OLEPTISS® 90 mg, 180 mg, 360 mg film-coated tablets.

OLEPTISS® 90 mg, 180 mg, 360 mg granules.

## 2 Description and composition

### Pharmaceutical forms

Dispersible tablets.

Film-coated tablets.

Granules.

### Active substance

Each dispersible tablet contains 100 mg / 125 mg / 250 mg / 400 mg / 500 mg deferasirox as active substance.

Each film-coated tablet contains 90 mg / 180 mg / 360 mg deferasirox as active substance.

Each sachet of granules contains 90 mg / 180 mg / 360 mg deferasirox as active substance.

### Excipients

#### Exjade® dispersible tablets

Lactose monohydrate; crospovidone; microcrystalline cellulose; povidone (K30); sodium lauryl sulphate; silicon dioxide; magnesium stearate

#### Oleptiss® film-coated tablets

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 carminine aluminum lake (E132).

## 3 Indication

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

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

## 4 Dosage and administration

### Transfusional iron overload

#### Exjade dispersible tablets

#### Dosage

It is recommended that therapy with Exjade be started after the transfusion of approximately 20 units (about 100 mL/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 microgram/L). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy.

#### Include the below text in the Exjade label only if both brands Exjade and Oleptiss are marketed together

For patients who are currently on chelation therapy with Oleptiss and switching to Exjade, the dose of Exjade should be 40% higher than the dose of Oleptiss, rounded to the nearest whole dispersible tablet.

#### Starting dose

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

An initial daily dose of 30 mg/kg may be considered for patients receiving more than 14 mL/kg/month of packed red blood cells (approximately >4 units/month for an adult), and for whom the objective is reduction of iron overload.

An initial daily dose of 10 mg/kg may be considered for patients receiving less than 7 mL/kg/month of packed red blood cells (approximately <2 units/month for an adult), and for whom the objective is maintenance of the body iron level.

For patients already well-managed on treatment with deferoxamine, a starting dose of Exjade that is numerically half that of the deferoxamine dose could be considered as shown in Tables 4-1 and 4-3 (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 20 mg/kg/day of Exjade).

#### Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of Exjade is adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range and to minimize the risk of overchelation (see section 6 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 Exjade may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated (see section 6 Warnings and precautions).

### **Oleptiss film-coated tablets and granules**

#### **Dosage**

It is recommended that therapy with Oleptiss 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 or sachet 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.

Oleptiss film-coated tablets and granules are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade dispersible tablet formulation (see section 11 Clinical Pharmacology). For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Oleptiss, the dose of Oleptiss should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet or sachet, as shown in Table 4-3.

#### **Starting dose**

The recommended initial daily dose of Oleptiss 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 Oleptiss that is numerically one third of the deferoxamine dose could be considered as shown in Tables 4-1 and 4-3 (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 Oleptiss).

#### **Dose adjustment**

It is recommended that serum ferritin be monitored every month and that the dose of Oleptiss 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 6 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 Oleptiss 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 6 Warnings and precautions).

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

**Table 4-1 Transfusional iron overload: Recommended doses**

	<b>Exjade Dispersible tablets</b>	<b>Oleptiss Film-coated tablets/granules</b>	<b>Transfusions</b>		<b>Serum ferritin</b>
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 to 6 months)	Increase				>2,500 microgram/L
	5 to 10 mg/kg/day Up to 40 mg/kg/day	3.5 to 7 mg/kg/day Up to 28 mg/kg/day			
	Decrease				
	5 to 10 mg/kg/day When target is reached	3.5 to 7 mg/kg/day			500 to 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 Table 4.3

## Non-transfusion-dependent thalassemia (NTDT) syndromes

### Exjade dispersible tablets

#### Dosage

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC)  $\geq 5$  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.

**Include the below text in the Exjade label only if both brands Exjade and Oleptiss are marketed together**

For patients who are currently on chelation therapy with Oleptiss and switching to Exjade, the dose of Exjade should be 40% higher than the dose of Oleptiss, rounded to the nearest whole dispersible tablet.

#### Starting dose

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



## Dose adjustment

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see section 6 Warnings and precautions). Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's LIC is  $\geq 7$  mg Fe/g dw, or serum ferritin is consistently  $>2,000$  microgram/L and not showing a downward trend, and the patient is tolerating the drug well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non-transfusion-dependent thalassemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is  $\leq 2,000$  microgram/L, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to  $>10$  mg/kg, dose reduction is recommended to 10 mg/kg or less when LIC is  $<7$  mg Fe/g dw or serum ferritin is  $\leq 2,000$  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.

### Oleptiss film-coated tablets and granules

## Dosage

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC)  $\geq 5$  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.

Oleptiss film-coated tablets and granules are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade dispersible tablet formulation (see section 11 Clinical pharmacology). For patients who are currently on chelation therapy with Exjade dispersible tablet and switching to Oleptiss, the dose of Oleptiss should be 30% lower than the dose of Exjade, rounded to the nearest whole tablet or sachet.

## Starting dose

The recommended initial daily dose of Oleptiss 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 6 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  $\geq 7$  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  $\leq 2,000$  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 4-2.

**Table 4-2 NTD: Recommended doses**

	Exjade Dispersible tablets	Oleptiss Film-coated tablets/granules	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 (every 3 to 6 months)	Increase		≥7 mg Fe/g dw	or	>2,000 microgram/L
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day	<7 mg Fe/g dw	or	≤2,000 microgram/L
Maximum dose	Decrease				
	5 to 10 mg/kg/day	3.5 to 7 mg/kg/day			
	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 DT and FCT/granules, as well as deferoxamine is shown in Table 4-3 below.

**Table 4-3 Dose conversion**

Deferoxamine dose**	Daily dose of Exjade Dispersible tablets	Daily dose for Oleptiss Film-coated tablets/granules
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

#### Exjade dispersible tablets

Exjade 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 10 mg/kg (see section 6 Warnings and precautions).

#### Oleptiss film-coated tablets and granules

Oleptiss 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 (see section 6 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%. Exjade/Oleptiss should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section 6 Warnings and precautions and section 11 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 6 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 6 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**

#### **Exjade dispersible tablets**

Exjade dispersible tablets must be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

#### **Oleptiss film-coated tablets**

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

Oleptiss 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 11 Clinical pharmacology).

#### **Oleptiss granules**

The granules should be 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. Oleptiss granules 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 11 Clinical pharmacology).

## **5 Contraindications**

Creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal.

High-risk myelodysplastic syndrome (MDS) patients and patients with other 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.

## 6 Warnings and precautions

The decision to remove accumulated iron should be individualized based on anticipated clinical benefit and risks of chelation therapy (see section 4 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 7 Adverse drug reactions). Although causal relationship with Exjade/Oleptiss could not be established, there have been rare cases of acute renal failure requiring dialysis or with fatal outcome.

It is recommended that serum creatinine and/or creatinine clearance be assessed in duplicate before initiating therapy, and monitored monthly thereafter.

Patients with pre-existing renal conditions or patients who are receiving medicinal products that may depress renal function may be more at risk of complications. Therefore, serum creatinine and/or creatinine clearance should be monitored weekly in the first month after initiation or modification of therapy (including switching formulation), and monthly thereafter. Caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections. Renal tubulopathy has been reported in patients treated with 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.

### **Use the below text only in the Exjade label**

For adult patients, the daily dose of Exjade may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes (see section 4 Dosage and administration). For pediatric patients, the dose may be reduced by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

**Use the below text only in the Oleptiss label**

For adult patients, the daily dose of Oleptiss 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 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, Exjade/Oleptiss should be interrupted. Therapy with Exjade/Oleptiss may be reinitiated depending on the individual clinical circumstances. The recommendations for renal function monitoring are summarized in the Table 6-1.

**Table 6-1 Recommendations for renal function monitoring**

	Serum creatinine		Creatinine clearance
<b>Before initiation of therapy</b>	Twice (2x)	and/or	Twice (2x)
<b>Contraindicated</b>	>2 times age-appropriate ULN*	or	<40 mL/min
<b>Monitoring</b>	<b>Monthly</b>	<b>and/or</b>	<b>Monthly</b>
	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:		
	<b>Weekly</b>	<b>and/or</b>	<b>Weekly</b>
<b>Reduction of daily dose by 10 mg/kg/day</b> (Exjade dispersible tablets), <b>and by 7 mg/kg/day</b> (Oleptiss film-coated tablets / granules), respectively			
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*		
<b>After dose reduction, interrupt treatment, if:</b>			
Adult and pediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		

\*ULN: upper limit of the normal range

**Hepatic Impairment**

Exjade/Oleptiss is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see sections 4 Dosage and administration and 11 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 11 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 7 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, Exjade/Oleptiss 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 Exjade/Oleptiss 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 7 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 Exjade/Oleptiss should be considered in patients who develop unexplained cytopenia. Re-introduction of therapy with Exjade/Oleptiss may be considered, once the cause of the cytopenia has been elucidated.

### **Gastrointestinal Disorders**

Gastrointestinal irritation may occur during Exjade/Oleptiss 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 7 Adverse drug reactions). Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Exjade/Oleptiss therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

Caution should be exercised in patients who are taking Exjade/Oleptiss in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants (see section 8 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 7 Adverse drug reactions). If reactions are severe, Exjade/Oleptiss should be discontinued and appropriate medical intervention instituted. Exjade/Oleptiss 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 Exjade/Oleptiss should be discontinued immediately and should not be reintroduced.

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

Skin rashes may appear during Exjade/Oleptiss treatment. For rashes of mild to moderate severity, Exjade/Oleptiss may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, Exjade/Oleptiss 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 7 Adverse drug reactions). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of Exjade/Oleptiss treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered .

## **Other considerations**

As with other iron chelator treatment, the risk of toxicity of Exjade/Oleptiss 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 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 and longitudinal growth in pediatric patients can be monitored at regular intervals (every 12 months).

### **Use the below text only for the dispersible tablet formulation (Exjade)**

The dispersible tablets contain lactose (1.1 mg lactose for each mg of deferasirox). This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

## **Driving and using machines**

No studies on the effects of Exjade/Oleptiss 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.



## 7 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 6 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 6 Warnings and precautions). The following adverse drug reactions, listed in Table 7-1, have been reported in clinical studies following treatment with deferasirox dispersible tablet. Adverse reactions are ranked below using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); 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 7-1 Adverse drug reactions reported in clinical studies**

<b>Psychiatric disorders</b>	
Uncommon:	anxiety, sleep disorder
<b>Nervous system disorders</b>	
Common:	headache
Uncommon:	dizziness
<b>Eye disorders</b>	
Uncommon:	cataract, maculopathy
Rare:	optic neuritis
<b>Ear and labyrinth disorders</b>	
Uncommon:	deafness
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon:	laryngeal pain
<b>Gastrointestinal disorders</b>	
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
<b>Hepatobiliary disorders</b>	
Common:	transaminases increased
Uncommon:	hepatitis, cholelithiasis
<b>Skin and subcutaneous tissue disorders</b>	
Common:	rash, pruritus
Uncommon:	pigmentation disorder
Rare:	erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)
<b>Renal and urinary disorders</b>	
Very common:	blood creatinine increased
Common:	proteinuria
Uncommon:	renal tubular disorder (Fanconi syndrome)
<b>General disorders and administration site conditions</b>	
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 7-2](#), are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

**Table 7-2 Adverse drug reactions derived from spontaneous reports (frequency not known)**

<b>Immune system disorders</b>	hypersensitivity reaction (including anaphylactic reaction and angioedema)
<b>Gastrointestinal disorders</b>	gastrointestinal perforation
<b>Hepatobiliary disorders</b>	hepatic failure
<b>Skin and subcutaneous tissue disorders</b>	Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
<b>Renal and urinary disorders</b>	renal tubular necrosis, acute renal failure (mostly serum creatinine increases $\geq 2x$ 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 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 6 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  $\geq 2$  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.

## 8 Interactions

### Agents that may decrease Exjade/Oleptiss 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 Exjade/Oleptiss with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade/Oleptiss efficacy. If Exjade/Oleptiss and a potent UGT inducer are used concomitantly, increases in the dose of Exjade/Oleptiss should be considered based on clinical response to therapy.

### Interaction with food

#### Exjade dispersible tablets

The bioavailability of deferasirox dispersible tablets was increased to a variable extent when taken along with food. Exjade must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see section 4 Dosage and administration).

#### Oleptiss film-coated tablets

The C<sub>max</sub> of deferasirox film-coated tablets was moderately increased (by 29%) when taken with a high-fat meal. Oleptiss may be taken either on an empty stomach or with a light meal (see section 11 Clinical pharmacology).

#### Oleptiss granules

There were no clinically relevant changes in deferasirox pharmacokinetics when deferasirox granules were administered with food.

### 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<sub>max</sub> 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 (deferrioxamine, 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 6 Warnings and precautions).

## **9 Pregnancy, lactation, females and males of reproductive potential**

### **9.1 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 Exjade/Oleptiss 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.

### **9.2 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 Exjade/Oleptiss is not recommended.

### **9.3 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 8 Interactions).

#### **Infertility**

Deferasirox did not affect fertility or reproduction in rat studies even at toxic doses.

## **10 Overdosage**

### **Exjade dispersible tablets**

Single doses up to 40 mg/kg 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.

#### **Oleptiss film-coated tablets and granules**

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

## **11 Clinical pharmacology**

Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC03

### **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 4 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 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)**

### **Oleptiss film-coated tablets**

Oleptiss 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<sub>max</sub> 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.

### **Oleptiss granules**

Oleptiss granules are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade dispersible tablet formulation. After strength-adjustment, the granule formulation (4 x 90 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<sub>max</sub> was increased by 34% (90% CI: 27.9% to 40.3%); however a clinical exposure/response analysis has revealed no evidence of clinically relevant effects of such an increase.

## **Absorption**

### **Exjade dispersible tablets**

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (T<sub>max</sub>) of about 1.5 to 4 hours. The absolute



bioavailability (AUC) of deferasirox (dispersible tablet formulation) was about 70% compared to an intravenous dose .

Total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approx. 13 to 25%) elevated when taken 30 minutes before meals with normal or high fat content. The total exposure (AUC) to deferasirox when taken after dispersion of tablets in orange juice or apple juice was equivalent to the exposure after dispersion in water (relative AUC ratios of 103% and 90%, respectively).

### **Oleptiss film-coated tablets**

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (T<sub>max</sub>) 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 Oleptiss 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<sub>max</sub> were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C<sub>max</sub> were increased (by 18% and 29%, respectively). The increases in C<sub>max</sub> 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 Oleptiss should be taken either on an empty stomach or with a light meal.

### **Oleptiss granules**

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (T<sub>max</sub>) 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 granules formulation has not been determined. Bioavailability of deferasirox with Oleptiss granules was 52% greater than that with Exjade dispersible tablets.

A food-effect study involving administration of the granules to healthy volunteers under fasting conditions and with a low-fat (fat content = approximately 30% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and C<sub>max</sub> were slightly decreased after a low-fat meal (by 10% and 11%, respectively). After a high-fat meal, only AUC was mildly increased (by 18%). When the granules were administered with applesauce or yogurt, a food effect was absent. It is recommended that Oleptiss 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<sub>1/2</sub>) ranged from 8 to 16 hours.

## **Linearity / non-linearity**

The C<sub>max</sub> and AUC<sub>0-24h</sub> 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<sub>max</sub> 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 4 Dosage and administration and section 6 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.

## 12 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 (deferroxamine) was conducted in patients with beta-thalassemia and transfusional hemosiderosis. Patients  $\geq 2$  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 deferroxamine 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 deferroxamine who had LIC values  $<7$  mg Fe/g dw were permitted to continue on their prior deferroxamine 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  $\geq 3$  mg Fe/g dw for baseline values  $\geq 10$  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 deferroxamine 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 deferroxamine with a difference of -13.5 in success rates and a 95% CI of [-21.6, -5.4]. Non-inferiority to deferroxamine 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 deferroxamine arm (Table 12-1). However, non-inferiority was demonstrated in a group of patients with baseline LIC levels  $\geq 7$  mg Fe/g dw who were allocated to the higher dose groups (deferasirox doses of 20 or 30 mg/kg and deferroxamine doses of  $\geq 35$  mg/kg). The success rates with deferasirox and deferroxamine 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  $\geq 7$  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 ( $-5.3 \pm 8.0$  mg Fe/g dw,  $p < 0.001$ , t-test) which was not statistically significantly different from deferroxamine ( $-4.3 \pm 5.8$  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 12-1).

**Table 12-1 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 observed hazard ratio of 0.64 (95% CI: 0.42, 0.96) suggests a positive impact of deferasirox on 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).

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  $\geq 56\%$ : 114 patients with baseline T2\* values  $>5$  to  $<20$  ms indicating myocardial siderosis (treatment cohort) and 78 patients with myocardial T2\*  $\geq 20$  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 to 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  $\pm$  coefficient of variation) significantly increased from a baseline value of 11.2 ms  $\pm$  40.5% to 12.9 ms  $\pm$  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  $\pm$  5.7% to 67.1  $\pm$  6.0%. In the prevention cohort, myocardial T2\* remained within the normal range and was unchanged from a baseline value of 32.0 ms  $\pm$  25.6% to 32.5 ms  $\pm$  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 12-2). 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 12-3).

**Table 12-2 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 12-3 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 12-4). Furthermore, a statistically significant dose effect of deferasirox was observed in favor of the 10 mg/kg/day dispersible tablet dose.

**Table 12-4 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)
<b>Change from baseline</b>			
<b>Number of evaluable patients</b>	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
<b>Difference of deferasirox - Placebo</b>			
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	-
<b>Difference of deferasirox 10 mg/kg - deferasirox 5 mg/kg</b>			
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 dispersible 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  $\geq 3$  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  $\geq 30\%$  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.

## 13 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.

See section 9 Pregnancy, lactation, females and males of reproductive potential.

## 14 Pharmaceutical information

### Incompatibilities

#### Exjade dispersible tablets

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

#### Oleptiss film-coated tablets/granules

Not applicable.

### Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture.

Information might differ in some countries.

Exjade/Oleptiss must be kept out of the reach and sight of children.

### Instructions for use and handling

No special requirements.

## 15 Supplier

Manufacturing site name and address: Sandoz S.R.L., Str. Livezeni Nr.7a, 540472, Targu Mures, Romania

## 16 Marketing Authorization Number

Oleptiss 90mg Film Coated Tablet – A4-100404

Oleptiss 180mg Film Coated Tablet – A4-100403

Oleptiss 360mg Film Coated Tablet - A4-100405