PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SIROXTRIN 125 dispersible tablets

SIROXTRIN 250 dispersible tablets

SIROXTRIN 500 dispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SIROXTRIN 125 contains 125 mg of deferasirox. Contains sugar (lactose monohydrate): 76,950 mg per dispersible tablet.

SIROXTRIN 250 contains 250 mg of deferasirox. Contains sugar (lactose monohydrate): 153,900 mg per dispersible tablet.

SIROXTRIN 500 contains 500 mg of deferasirox. Contains sugar (lactose monohydrate): 307,800 mg per dispersible tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

SIROXTRIN 125: White to off-white coloured flat round uncoated tablets with bevelled edges, debossed with ‘489’ on one side and plain on other side.

SIROXTRIN 250: White to off-white coloured flat round uncoated tablets with bevelled edges, debossed with ‘490’ on one side and plain on other side.

SIROXTRIN 500: White to off-white coloured flat round uncoated tablets with bevelled edges, debossed with ‘491’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

SIROXTRIN therapy should only be initiated when there is evidence of iron overload (liver iron concentration (LIC) ≥ 5 mg Fe/g dry weight (dw) or serum ferritin consistently > 800 microgram/L).

4.2 Posology and method of administration

Posology

Transfusional iron overload

Dosage

It is recommended that therapy with SIROXTRIN 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. SIROXTRIN is available in three tablet strengths (125 mg, 250 mg and 500 mg).

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

Starting dose

The starting dose is determined by the frequency of blood transfusions.

The recommended initial daily dose of SIROXTRIN 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).

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).

For patients already well-managed on treatment with deferoxamine, a starting dose of SIROXTRIN that is numerical half that of the deferoxamine dose could be considered (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 SIROXTRIN).

Non-transfusion-dependent thalassaemia syndrome

Dosage

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

Starting dose

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

Dose adjustment

It is recommended that serum ferritin be monitored every month to assess the patients' response to therapy and to minimize the risk of overchelation (see section 4.3). Every 3 to 6 months of treatment, consider a dose increase in increments of 5 to 10 mg/kg if the patient's

LIC is ≥ 7 mg Fe/g dw, or serum ferritin is consistently > 2 000 microgram/L and not showing a downward trend, and the patient is tolerating the medicine 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 thalassaemia syndromes.

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

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

Once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 microgram/L), treatment should be interrupted. Treatment should be re-initiated when there is evidence from clinical monitoring that chronic iron overload is present.

Special populations

Elderly patients

The dosing recommendations for elderly patients are the same as described above. Elderly patients experienced a higher frequency of adverse reactions than younger patients and elderly patients should be monitored closely for adverse reactions that may require a dose adjustment.

Patients with renal impairment

SIROXTRIN treatment must be used with caution in patients with serum creatinine levels above the age-appropriate upper limit of the normal range (see section 4.3)

SIROXTRIN should not be used by patients with CrCl below 60 ml/min. (see section 4.3)

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 4.4).

For adult patients, the daily dose of SIROXTRIN 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.

For paediatric patients, the dose may be reduced by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

If there is a progressive increase in serum creatinine beyond the upper limit of normal, SIROXTRIN should be interrupted. Therapy with SIROXTRIN may be reinitiated depending on the individual clinical circumstances.

Patients with hepatic impairment

For patients with moderate hepatic impairment (Child-Pugh B), the starting dose should be reduced by approximately 50 %. SIROXTRIN should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3).

Hepatic function in all patients should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter (see section 4.4).

Paediatric population

The dosing recommendations for paediatric patients are the same as for adult patients. It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation (see section 4.4). Changes in weight of paediatric patients over time must be taken into account when calculating the dose.

Method of administration

SIROXTRIN 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 – 200 ml) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be resuspended in a small volume of water or juice and swallowed.

The tablets must not be chewed or swallowed whole (see section 4.5).

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

4.3 Contraindications

- Hypersensitivity to deferasirox or to any of the other excipients (see section 6.1).
- Creatinine clearance < 60 ml/min.
- Repaglinide (see section 4.5).
- High risk myelodysplastic syndrome (MDS) patients and patients with other haematological and nonhaematological malignancies with limited expected survival (< 1 year) who are not expected to benefit from chelation therapy due to the rapid progression of their disease.
- Severe hepatic impairment (Child-Pugh C).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

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

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

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

Renal impairment

Non-progressive rises in serum creatinine have been noted in patients treated with SIROXTRIN, usually within the normal range. Cases of acute renal failure have been reported (see section 4.8). Although causal relationship with SIROXTRIN could not be established, there have been cases of acute renal failure requiring dialysis or with fatal outcome.

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

Patients with pre-existing renal conditions or patients who are receiving other medicines that may depress renal function may be more at risk of complications and weekly monitoring of serum creatinine and/or creatinine clearance is recommended in the first month after initiation or modification of therapy (including switching formulation) and monthly thereafter. SIROXTRIN should not be used in patients with creatinine clearance less than 60 mL/min (see section 4.3).

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

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

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

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

The recommendations for renal function monitoring are summarized in the Table 1.

Table 1: Recommendations for renal function monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and/or	Twice (2x)
Contraindicated	> 2 times age appropriate ULN*	or	< 40 mL/min
Monitoring	**Monthly**	**and/or**	**Monthly**
	For patients with pre-existing renal conditions, or patients who are receiving medicines that may depress the renal function as they may be more at risk of complications in the first month after initiation, or modification of therapy (including switching formulation), monitoring should be:		
	Weekly	**and/or**	**Weekly**
Reduction of daily dose by 10 mg/kg/day			
if following renal parameters are observed on two consecutive visits and cannot be attributed to other causes:			
Adult patients	> 33 % above pre-treatment average		

	(non-progressive rise)		
Paediatric patients	> age-appropriate ULN*		
After dose reduction, interrupt treatment, if:			
Adult and paediatric patients	Progressive increase in serum creatinine beyond the upper limit of normal		
*ULN: upper limit of the normal range			

Hepatic

SIROXTRIN is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3). Deferasirox is principally eliminated by glucuronidation and is minimally (about 8 %) metabolised by oxidative cytochrome P450 enzymes.

Although uncommon (0,3 %), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed. There have been post marketing reports of hepatic failure in patients treated with deferasirox (as in SIROXTRIN). Most reports of hepatic failure involved patients with significant comorbidities including liver cirrhosis and multi-organ failure; fatal outcomes were reported in some of these patients.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, SIROXTRIN 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 SIROXTRIN treatment at a lower dose followed by gradual dose escalation may be

considered.

Table 2: Summary of safety monitoring recommendations

Test	Frequency
Serum creatinine	In duplicate prior to therapy. Weekly during first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy or after dose modification (including switch of formulation). Monthly thereafter.
Proteinuria	Prior to therapy. Monthly thereafter.
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual	Prior to therapy.

development	Annually in paediatric patients.

Gastrointestinal

Gastrointestinal irritation may occur during SIROXTRIN treatment. Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox (as in SIROXTRIN). There have been rare reports of fatal GI haemorrhage, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts. Multiple ulcers have been observed in some patients. Medical practitioners and patients should remain alert for signs and symptoms of GI ulceration and haemorrhage during SIROXTRIN 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 SIROXTRIN in combination with medicines that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts $< 50 \times 10^9$/L.

Skin disorders

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinaphilia and systemic symptoms (DRESS) which could be life-threatening or fatal. Patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If any SCAR is suspected SIROXTRIN should be discontinued immediately and should not be reintroduced.

Cases of erythema multiforme have been reported during deferasirox (as in SIROXTRIN) treatment.

Skin rashes may appear during SIROXTRIN treatment. For rashes of mild to moderate severity,

SIROXTRIN may be continued without dose adjustment, since the rash often resolves spontaneously. For more severe rash, where interruption of treatment may be necessary, SIROXTRIN may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction may be conducted in combination with a short period of oral steroid administration.

Hypersensitivity reactions

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

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox (as in SIROXTRIN) treatment (see section 4.8). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of SIROXTRIN treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.

Blood disorders

There have been post marketing reports (both spontaneous and from clinical trials) of anaemia or detection of anaemia and other cytopenias in patients treated with deferasirox (as in SIROXTRIN). Although most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure (see section 4.8) the contribution of SIROXTRIN

could not always be excluded.

Blood counts should be monitored regularly. Dose interruption of treatment with SIROXTRIN should be considered in patients who develop unexplained anaemia or other cytopenias. Reintroduction of therapy with SIROXTRIN may be considered once the cause of the cytopenia has been elucidated.

Growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected (see section 4.8). However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored prior to therapy and at regular intervals (every 12 months).

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. Closer monitoring of serum ferritin levels, as well as renal and hepatic function is recommended during periods of treatment with high doses and when serum ferritin levels are close to the target range. Dose reduction may be considered to avoid overchelation (see section 4.2).

The results of the tests for serum creatinine, serum ferritin and serum transaminases should be recorded and regularly assessed for trends.

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with SIROXTRIN.

Lactose

SIROXTRIN contains lactose. Patients with the rare hereditary condition of galactose

intolerance, e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SIROXTRIN.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Anticipated interactions resulting in a concomitant use not recommended

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

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

Interaction with midazolam and other medicines metabolised by CYP3A4

In a healthy volunteer study, the concomitant administration of deferasirox (as in SIROXTRIN) and midazolam (a CYP3A4 substrate) resulted in a decrease of midazolam exposure by 17 % (90 % CI: 8 % - 26 %). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with medicines metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive medicines).

Medicines that may decrease SIROXTRIN systemic exposure

In a healthy volunteer study, the concomitant administration of deferasirox (as in SIROXTRIN) (single dose of 30 mg/kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by

44 % (90 % CI: 37 % - 51 %). Therefore, the concomitant use of SIROXTRIN with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in SIROXTRIN efficacy. If SIROXTRIN and a potent UGT inducer are used concomitantly, increases in the dose of SIROXTRIN should be considered based on clinical response to therapy.

Interaction with repaglinide and other medicines metabolised by CYP2C8

In a healthy volunteer study, the concomitant administration of deferasirox (as in SIROXTRIN) (repeated dose of 30 mg/kg/day) and the CYP2C8 substrate repaglinide (single dose of 0,5 mg) resulted in an increase in repaglinide AUC and C_{max} by 131 % (90 % CI: 103 % - 164 %) and 62 % (90 % CI: 42 % - 84 %), respectively. An interaction between SIROXTRIN and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other medicines metabolized by CYP1A2

In a healthy volunteer study, the concomitant administration of deferasirox (as in SIROXTRIN) (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase in theophylline AUC by 84 % (90 % CI: 73 % to 95 %). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing.

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.

When deferasirox (as in SIROXTRIN) and theophylline are used concomitantly, monitoring of theophylline concentration and possible theophylline dose reduction should be considered. An interaction between SIROXTRIN and other CYP1A2 substrates may be possible.

Interaction with food

The bioavailability of deferasirox (as in SIROXTRIN) was increased to a variable extent when taken along with food. SIROXTRIN must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see section 4.2).

Information on dispersion of SIROXTRIN in fruit juices other than orange and apple is not available.

Other information

No interaction was observed between deferasirox (as in SIROXTRIN) and digoxin in healthy volunteers. The concomitant administration of deferasirox (as in SIROXTRIN) and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/day have not been associated with adverse consequences.

The safety profile of deferasirox in combination with other iron chelators (deferoxamine, deferiprone) observed in clinical trials, post-marketing experience or published literature (as applicable) was consistent with that characterized for monotherapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. SIROXTRIN should not be used during pregnancy (see section 4.3).

Breastfeeding

In animal studies, deferasirox (as in SIROXTRIN) was found to be rapidly and extensively secreted into maternal milk. It is not known if SIROXTRIN is secreted into human milk. Breastfeeding while taking SIROXTRIN is not recommended.

Fertility

No fertility data is available for humans. In animals, no adverse effects on male or female fertility were found.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent reactions reported during chronic treatment with deferasirox (as in SIROXTRIN) in adult and paediatric patients included gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea, or abdominal pain), and skin rash. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly.

These reactions are dose dependent. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in 36 % of patients.

These reactions are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose (see section 4.4).

b. Tabulated summary of adverse reactions

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequency unknown	Pancytopenia, thrombocytopenia, neutropenia, aggravated anaemia
Immune system disorders	Frequency unknown	Hypersensitivity reactions (including anaphylaxis and angioedema)
Metabolism and nutrition disorders	Frequency unknown	Metabolic acidosis
Psychiatric disorders	Less frequent	Anxiety, sleep disorder
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness
Eye disorders	Less frequent	Early cataract, maculopathy, optic neuritis
Ear and labyrinth disorders	Less frequent	Hearing loss
Respiratory, thoracic and mediastinal disorders	Less frequent	Pharyngolaryngeal pain
Gastrointestinal disorders	Frequent	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
	Less frequent	Gastritis, gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, oesophagitis

	Frequency unknown	Gastrointestinal perforation, acute pancreatitis
Hepato-biliary disorders	Frequent	Increased transaminases
	Less frequent	Hepatitis, cholelithiasis
	Frequency unknown	Hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritis
	Less frequent	Pigmentation disorder, drug reaction with eosinophilia and systemic symptoms (DRESS)
	Frequency unknown	Stevens-Johnson syndrome, leukocytoclastic vasculitis, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN)
Renal and urinary disorders	Frequent	Increased blood creatinine, proteinuria
	Less frequent	Glycosuria, renal tubulopathy (Fanconi's syndrome)
	Frequency unknown	Nephrolithiasis, renal tubular necrosis, acute renal failure (serum creatinine increases > 2 x upper limit of normal), tubulointerstitial nephritis
General disorders and administration site conditions	Less frequent	Pyrexia, oedema, fatigue

c. Paediatric population

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

In a 5-year observational study in which 267 children aged 2 to < 6 years (at enrolment) with transfusional hemosiderosis received deferasirox, there were no unexpected safety findings regarding adverse events (AEs) or laboratory abnormalities. Increases in serum creatinine of > 33 % and above the upper limit of normal (ULN) on ≥ 2 consecutive occasions were observed in 3,1 % of children and elevation of alanine aminotransferase (ALT) greater than 5 times the ULN was reported in 4,3 % of children. The most frequently observed AEs with reported suspected relationship to study medicine were increase in ALT (21,1 %), increase in aspartate aminotransferase (AST, 11,9 %), vomiting (5,4 %), rash (5,0 %), increase in blood creatinine (3,8 %), abdominal pain (3,1 %) and diarrhoea (1,9 %). Overall growth and development were not affected in this paediatric population.

Reporting of suspected adverse reactions

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

4.9 Overdose

Single doses up to 40 mg/kg in normal participants have been well tolerated.

Early sign of acute overdose are digestive effects such as abdominal pain, diarrhoea, nausea and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome with resolved after treatment.

There is no specific antidote for deferasirox. Symptomatic and supportive treatment should be initiated as appropriate to the patient's clinical status. Symptomatic treatment, as medically appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 27 Chelating agents (versenates) as heavy metal antidotes.

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC03.

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

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

5.2 Pharmacokinetic properties

Absorption

Deferasirox is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1,5 to 4 hours. The absolute bioavailability (AUC) of deferasirox from deferasirox tablets is 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 – 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).

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 faeces (84 % of the dose). Renal excretion of deferasirox and its metabolites is minimal (8 % of the dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours.

Linearity/non-linearity

The C_{max} and AUC_{0-24h} of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1,3 to 2,3.

Special populations

Paediatric patients

The overall exposure of adolescents (12 to ≤ 17 years) and children (2 to < 12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was about 50 % lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Gender

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

Elderly patients

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

Renal or hepatic impairment

In a single dose study, the average AUC of deferasirox in 6 participants with mild hepatic impairment (Child-Pugh A) increased 16 % over that found in 6 participants with normal hepatic function, while the average AUC of deferasirox in 6 participants with moderate hepatic impairment (Child-Pugh B) increased 76 % over that found in 6 participants with normal hepatic function. The average C_{max} of deferasirox in participants with mild or moderate hepatic impairment increased 22 % over that found in participants with normal hepatic function. Deferasirox should not be used in patient with severe hepatic impairment (Child-Pugh C). The pharmacokinetics of deferasirox have not been studied in patients with renal impairment.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Purified water

Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

SIROXTRIN is packed in Alu-Alu blisters (10 tablets per blister) or in HDPE bottles with a child-resistant closure. Pack size: 30 or 100 dispersible tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

3 Gwen Lane

Fourth Floor, Sandton

2031

South Africa

8 REGISTRATION NUMBERS

SIROXTRIN 125: 561222

SIROXTRIN 250: 561223

SIROXTRIN 500: 561224

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 March 2025

10 DATE OF REVISION OF THE TEXT

17 June 2024