AVERROES PHARMA
FOR PHARMACEUTICAL INDUSTRIES

Ronisirox

Deferasirox 500 mg
Tablet for oral suspension
▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Each tablet contains: Deferasirox 500 mg as active ingredients and the following as inactive ingredients:
Lactose monohydrate, microcrystalline cellulose, povidone K30, sodium lauryl sulfate, crospovidone, colloidal anhydrous silica, magnesium stearate.

Precautions & Warning

Renal Impairment, including Failure
· Hepatic Impairment, including Failure
· Gastrointestinal Hemorrhage

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes (MDS), underlying renal or hepatic impairment or low platelet counts (<50 x 109/L). Ronisirox therapy requires close patient monitoring, including measurement of:
• serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter;
• Serum transaminases and bilirubin prior to initiation of therapy, every two weeks during the first month and monthly thereafter.

Clinical particulars

Therapeutic indications

Ronisirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

Ronisirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

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

Ronisirox is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Posology and method of administration

Treatment with Ronisirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload.

Posology- transfusional iron overload

It is recommended that treatment be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells (PRBC) or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 µg/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.

In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40% higher than the dose of film-coated tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 1 Recommended doses for transfusional iron overload

	Film-coated tablets	**Dispersible tablets**	**Transfusions**		**Serum ferritin**
Starting dose	14 mg/kg/day	20 mg/kg/day	After 20 units (about 100 ml/kg) of PRBC	or	>1,000 µg/l
Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)		
	7 mg/kg/day	10 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)		
For patients well managed on deferoxamine	One third of deferoxamine dose	Half of deferoxamine dose			
Monitoring					**Monthly**
Target range					**500-1,000 µg/**l
Adjustment steps	**Increase**				>2,500 µg/l
(every 3-6 months)	3.5 - 7 mg/kg/day Up to 28 mg/kg/day	5-10 mg/kg/day Up to 40 mg/kg/day			
	Decrease				

	3.5 - 7 mg/kg/day	5-10 mg/kg/day		<2,500 µg/l
	In patients treated with doses >21 mg/kg/day	In patients treated with doses >30 mg/kg/day		
	- When target is reached			500-1,000 µg/l
Maximum dose	**28 mg/kg/day**	**40 mg/kg/day**		
Consider interruption				**<500 µg/l**

Starting dose

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

An initial daily dose of 30 mg/kg may be considered for patients who require reduction of elevated body iron levels and who are also 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 who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.

For patients already well managed on treatment with deferoxamine, a starting dose of Ronisirox that is numerically 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 Ronisirox). When this results in a daily dose less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of Ronisirox be 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 2,500 µg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. If only very poor haemosiderosis control is achieved at doses up to 30 mg/kg, a further increase (to a maximum of 40 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 30 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 30 mg/kg, dose reductions in steps of 5 to 10 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

Posology - non-transfusion-dependent thalassaemia syndromes

Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients.

In case of switching from film-coated tablets to dispersible tablets, the dose of dispersible tablets should be 40% higher than the dose of film-coated tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 2 Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	**10 mg/kg/day**	≥5 mg Fe/g dw	or	>800 µg/l
Monitoring					**Monthly**
Adjustment steps	**Increase**		≥7 mg Fe/g dw	or	>2,000 µg/l
(every 3-6 months)	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10 mg/kg/day**			
	For adults		not assessed	and	≤2,000 µg/l
	For paediatric patients				
Interruption			**<3 mg Fe/g dw**	or	**<300 µg/l**
Retreatment			**Not recommended**		

*LIC is the preferred method of iron overload determination.

Starting dose

The recommended initial daily dose of Ronisirox in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment

It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg

should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product 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 µg/l, dosing should not exceed 10 mg/kg.
For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 µg/l.

Treatment cessation

Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/l), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.

Special populations

Elderly patients (≥65 years of age)

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 (in particular, diarrhea) and should be monitored closely for adverse reactions that may require a dose adjustment.

Pediatric population

Transfusional iron overload:

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

Non-transfusion-dependent thalassaemia syndromes:

In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 10 mg/kg. In these patients, closer

monitoring of LIC and serum ferritin is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤800 µg/l.

Children from birth to 23 months:

The safety and efficacy of DEFERASIROX in children from birth to 23 months of age have not been established. No data are available.

Patients with renal impairment

Ronisirox has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min.

Patients with hepatic impairment

Ronisirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50%, and Ronisirox must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month.

Method of administration

For oral use.

Ronisirox 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 orange or apple juice (100 to 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Combination with other iron chelator therapies as the safety of such combinations has not been established.
Patients with estimated creatinine clearance <40 ml/min.or serum creatinine > 2 times the age appropriate upper limit of normal.
Poor Performance status and high-risk MDS or Advanced Malignancies.
· Platelets counts< 50 x 10^9 /L.

Special warnings and precautions for use

Renal function:
Ronisirox has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.
During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Cases of acute renal failure have been reported following post-marketing use of Ronisirox .In some post-marketing cases, renal function deterioration has led to renal failure requiring temporary or permanent dialysis.
The causes of the rises in serum creatinine have not been elucidated. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function, and in patients who are receiving high doses of Ronisirox and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult). While no increase in renal adverse events was observed after dose escalation to doses above 30 mg/kg in clinical trials, an increased risk of renal adverse events with Ronisirox doses above 30 mg/kg cannot be excluded.

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, creatinine clearance** (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels **should be monitored weekly in the first month after initiation or modification of therapy with Ronisirox, and monthly thereafter**. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhea or vomiting.
There have been post-marketing reports of metabolic acidosis occurring during treatment with deferasirox. The majority of these patients had renal impairment, renal tubulopathy (Fanconi's syndrome) or diarrhea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of deferasirox therapy should be considered in patients who develop metabolic acidosis.

Table 3 Dose adjustment and interruption of treatment for renal monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			**<60 ml/min**
Monitoring			
- First month after start of therapy or dose modification	Weekly	and	Weekly
- Thereafter	Monthly	and	Monthly
Reduction of daily dose by 10 mg/kg/day (dispersible tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			

Adult patients	>33% above pre-treatment average	and	Decreases <LLN* (<90 ml/min)
Paediatric patients	> age appropriate ULN**	and/or	Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range **ULN: upper limit of the normal range			

Treatment may be reinitiated depending on the individual clinical circumstances.

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

• Proteinuria (test should be performed prior to therapy and monthly thereafter)

• Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox.

Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:

• Serum creatinine remains significantly elevated and

• Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome).

Hepatic function:

Liver function test elevations have been observed in patients treated with Ronisirox. Post marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with Ronisirox. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However, the role of Ronisirox as a contributing or aggravating factor cannot be excluded.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked 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, Ronisirox 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 treatment at a lower dose followed by gradual dose escalation may be considered.

Ronisirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Summary of safety monitoring recommendations:

Test	**Frequency**
Serum creatinine	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification.

	Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy and during first month after dose modification. 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 development	Prior to therapy. Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of Ronisirox might be limited and may be inferior to risks. As a consequence, treatment with Ronisirox is not recommended in these patients.
Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).
Data in children with non-transfusion-dependent thalassaemia are very limited. As a consequence, Ronisirox therapy should be closely monitored to detect side effects and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with Ronisirox, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal disorders

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving Ronisirox. Multiple ulcers have been observed in some patients. There have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during Ronisirox therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. Caution should be exercised in patients who are taking Ronisirox in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm^3 (50 x 10^9/l).

Skin disorders

Skin rashes may appear during Ronisirox treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration. Cases of Stevens-Johnson syndrome (SJS) have been reported post marketing. If SJS is suspected, Ronisirox should be discontinued immediately and should not be reintroduced.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Ronisirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If such reactions occur, Ronisirox should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock.

Vision and hearing

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

Blood disorders

There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with Ronisirox. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy .If serum ferritin falls consistently below 500 µg/l (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), an interruption of treatment should be considered.

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 Ronisirox.

Each tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency should not take this medicine.

Interaction with other medicinal products and other forms of interaction

The safety of Ronisirox in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies.

Interaction with food

The bioavailability of deferasirox was increased to a variable extent when taken along with food. Ronisirox dispersible tablets must therefore be taken on an empty stomach at least 30 minutes before food, preferably at the same time each day.

Agents that may decrease Ronisirox systemic exposure

Deferasirox metabolism depends on UGT enzymes. Therefore, the concomitant use of Ronisirox with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in Ronisirox efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of Ronisirox adjusted if necessary.

Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling.

Interaction with midazolam and other agents metabolised by CYP3A4

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

Interaction with repaglinide and other agents metabolised by CYP2C8

In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily, dispersible tablet formulation), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, increased repaglinide AUC and C_{max} about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]), respectively. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed. An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolised by CYP1A2

In a healthy volunteer study, the concomitant administration of deferasirox as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of 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. Therefore, the concomitant use of deferasirox with theophylline is not recommended. If deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

Other information

The concomitant administration of deferasirox and aluminium-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox tablets with aluminium-containing antacid preparations.

The concomitant administration of deferasirox with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates

may increase the risk of gastrointestinal toxicity. The concomitant administration of deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown.

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

Ronisirox may decrease the efficacy of hormonal contraceptives. Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using ronisirox.

Breast-feeding

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

Fertility

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

Effects on ability to drive and use machines

No studies on the effects of Ronisirox on the ability to drive and use machines have been performed. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The most frequent reactions reported during chronic treatment with Ronisirox in adult and pediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash in about 7% of patients. Diarrhoea is reported more commonly in pediatric patients aged 2 to 5 years and in the elderly. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

Tabulated list of adverse reactions

Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing

Table 4

Blood and lymphatic system disorders	
Not known:	Pancytopenia[1], thrombocytopenia[1], anaemia aggravated[1], neutropenia
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylaxis and angioedema)[1]

Metabolism and nutrition disorders	
Not known:	Metabolic acidosis
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Early cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis
Rare:	Oesophagitis
Not known:	Gastrointestinal perforation
Hepatobiliary disorders	
Common:	Transaminases increased

Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure[1]
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Not known:	Stevens-Johnson syndrome[1], leukocytoclastic vasculitis[1], urticaria[1], erythema multiforme[1], alopecia[1]
Renal and urinary disorders	
Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubulopathy (acquired Fanconi's syndrome), glycosuria
Not known:	Acute renal failure[1], tubulointerstitial nephritis[1], nephrolithiasis, renal tubular necrosis[1]
General disorders and administration site conditions	
Uncommon:	Pyrexia, oedema, fatigue

[1] Adverse reactions reported during postmarketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

Pediatric population

Diarrhoea is reported more commonly in pediatric patients aged 2 to 5 years than in older patients.
Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

info@averroes-eg.com

Or on the following address:

- Block No 6048, 6th industrial zone Sadat city, Egypt. Tel: 0482630201/2
- 55 Hafez badawy street Nasr city, Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)
21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-Mail: pv.center@eda.mohp.gov.eg
Fax Number: +2 02 23684194
Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No.1303

Overdose

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea.

Acute signs of overdose may include nausea, vomiting, headache and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agent.

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 faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Pharmacodynamic effects

In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, Ronisirox at daily doses of 10, 20 and 40 mg/kg induced the mean net excretion of 0.119, 0.329 and 0.445 mg Fe/kg body weight/day, respectively.

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 Ronisirox 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.

Distribution

Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres 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: in a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

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*.

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. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

Linearity / non-linearity

The C_{max} and $AUC_{0\text{-}24h}$ 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.

Characteristics in patients

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

AVERROES PHARMA
FOR PHARMACEUTICAL INDUSTRIES

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

The pharmacokinetics of deferasirox have not been studied in patients with renal impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

HOW SUPPLIED/STORAGE AND HANDLING

Carton box contains 1 Al/ PVC Strip of 10 tablets + inner leaflet

Storage: Store at temperature not exceeding 30°C; in dry place

(THIS IS A MEDICAMENT)

-Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-Do not by yourself interrupt the period of treatment prescribed.
-Do not repeat the same prescription without consulting your doctor.

Manufactured by: Averroes Pharma for pharmaceutical industries
Block no. (6048) 6th industrial zone - Sadat city, Egypt.