Front

Dasirox®

(D e f e r a s i r o x) Tablet

ڈیسی روکس

COMPOSITION:

Dasirox tablet 100 mg:
Each dispersible tablet contains:
Deferasirox ..... 100 mg.

Product Specs.: Innovator

Dasirox tablet 250 mg:
Each dispersible tablet contains:
Deferasirox ..... 250 mg.

Product Specs.: Innovator

Dasirox tablet 400 mg:
Each dispersible tablet contains:
Deferasirox ..... 400 mg.

Product Specs.: Innovator

Dasirox tablet 500 mg:
Each dispersible tablet contains:
Deferasirox ..... 500 mg.

Product Specs.: Innovator

DESCRIPTION:
Deferasirox is an iron chelating agent.

CLINICAL PHARMACOLOGY:
Mechanism of action:
Deferasirox is an orally active chelator that is selective for iron (as Fe3+). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although Deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of Deferasirox. The clinical significance of these decreases is uncertain.
Pharmacokinetics:
Absorption: Deferasirox is absorbed following oral administration with median times to maximum plasma concentration (T_{max}) of about 1.5-4 hours. The C_{max} and AUC of Deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to Deferasirox increased by an accumulation factor of 1.3-2.3 after multiple doses. The absolute bioavailability (AUC) of Deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (AUC) of Deferasirox was variably increased when taken with a meal.
Distribution: Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of Deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (Vss) of Deferasirox is 14.37 ± 2.69 L in adults.
Metabolism: Glucuronidation is the main metabolic pathway for Deferasirox, with subsequent biliary excretion.
Excretion: Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of Deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half life($t_{1/2}$) ranged from 8-16 hours following oral administrations.

DRUG INTERACTIONS:
Aluminum containing antacid preparations:
Avoid use of Deferasirox with aluminum-containing antacid preparations due to the mechanism of action of Deferasirox.
Agents Metabolized by CYP3A4:
Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are co-administered. Closely monitor patients for signs of reduced effectiveness when Deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil).
Agents Metabolized by CYP2C8:
Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are co-administered. If Deferasirox and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when Deferasirox is co-administered with other CYP2C8 substrates.
Agents metabolized by CYP1A2:
Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are co-administered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with Deferasirox. Monitor theophylline concentrations and consider theophylline dose modification if you must co-administer theophylline with Deferasirox. Closely monitor patients for signs of exposure related toxicity when Deferasirox is co-administered with other drugs metabolized by CYP1A2.
Agents inducing UDP-glucuronosyltransferase (UGT) metabolism:
Deferasirox is a substrate of UGT1A1 and to a lesser extent UGT1A3. The concomitant use of Deferasirox with potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Deferasirox efficacy due to a possible decrease in Deferasirox concentration. Avoid the concomitant use of potent UGT inducers with Deferasirox. Consider increasing the initial dose of Deferasirox if you must co-administer these agents together.
Bile acid sequestrants:
Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Deferasirox due to a possible decrease in Deferasirox concentration. If you must co-administer these agents together, consider increasing the initial dose of Deferasirox.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Pregnancy Category C:
There are no adequate and well-controlled studies with Deferasirox in pregnant women.

Nursing mothers:
It is not known whether Deferasirox is excreted in human milk.
Pediatric use:
The safety and efficacy of Deferasirox in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults. Safety and effectiveness have not been established in pediatric patients with chronic iron overload due to blood transfusions who are less than 2 years of age or pediatric patients with chronic iron overload and non-transfusional-dependent thalassemia who are less than 10 years of age.
Geriatric use:
Monitor elderly patients for early signs or symptoms of adverse reactions that may require a dose adjustment. Elderly patients are at increased risk for toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.
Renal impairment:
The safety, efficacy and pharmacokinetics of Deferasirox have not been studied in patients with renal impairment. Deferasirox can cause renal failure. Monitor serum creatinine and calculate creatinine clearance (using Cockcroft-Gault method) during treatment in all patients. Reduce, interrupt or discontinue Deferasirox dosing based on increases in serum creatinine . Deferasirox is contraindicated in patients with a creatinine clearance < 40 mL/min or serum creatinine > 2 times the age-appropriate upper limit of normal.
Hepatic impairment:
In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, Deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC of Deferasirox increased 16% in 6 subjects with mild (Child-Pugh A) hepatic impairment, and 76% in 6 subjects with moderate (Child-Pugh B) hepatic impairment compared to 6 subjects with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only one subject. Avoid the use of Deferasirox in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, the starting dose should be reduced by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration.

INDICATIONS AND USAGE:
Treatment of chronic iron overload due to blood transfusions (transfusional iron overload) in patients 2 years of age and older.
Treatment of chronic iron overload in non-transfusion dependent thalassemia syndromes: in patients 10 years of age and older with non-transfusion dependent thalassemia syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of LIC less than 5 mg Fe/gdw.
Limitation of use: The safety and efficacy of Deferasirox when administered with other iron chelating agents have not been established.

DOSAGE AND ADMINISTRATION:
Transfusional iron overload: Deferasirox therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20 units of packed red blood cells for a 40-kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.
Prior to starting therapy, obtain:
- Serum ferritin level
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method)
- Serum transaminases and bilirubin
- Baseline auditory and ophthalmic examinations

The recommended initial dose of Deferasirox for patients 2 years of age and older is 20 mg per kg body weight orally, once daily. Calculate doses (mg/kg/day) to the nearest whole tablet. After commencing therapy, monitor serum ferritin monthly and adjust the dose of Deferasirox, if necessary, every 3-6 months based on serum ferritin trends. Make dose adjustments in steps of 5 or 10 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 30 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 40 mg per kg may be considered. Doses above 40 mg per kg are not recommended.
If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with Deferasirox.
Iron overload in Non-transfusion dependent thalassemia syndromes:
Deferasirox therapy should only be considered when a patient with a non-transfusion dependent thalassemia syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.
Prior to starting therapy, obtain:
- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with Deferasirox therapy
- Serum ferritin level on at least 2 measurements one month apart.
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method)
- Serum transaminases and bilirubin
- Baseline auditory and ophthalmic examinations

Initiating therapy:
- The recommended initial dose of Deferasirox is 10 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 20 mg/kg/day after 4 weeks.

During therapy:
- Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of Deferasirox to a maximum of 20 mg/kg/day. Do not exceed a maximum of 20 mg/kg/day.
- If after 6 months of therapy, the LIC is 3-7 mg Fe/g dw, continue treatment with Deferasirox at no more than 10 mg/kg/day.
- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with Deferasirox and continue to monitor the LIC.
- Monitor blood counts, hepatic function, and renal function.
- Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

ADMINISTRATION:
Do not chew tablets or swallow them whole. Take Deferasirox once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Completely disperse tablets by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Disperse doses of less than 1 g in 3.5 ounces of liquid and doses of 1 g or greater in 7 ounces of liquid. After swallowing the suspension, re-suspend any residue in a small volume of liquid and swallow. Do not take Deferasirox with aluminum-containing antacid products.
Use in patients with baseline hepatic or renal impairment:
Patients with baseline hepatic impairment:
Mild (Child-Pugh A) hepatic impairment: No dose adjustment is necessary.
Moderate (Child-Pugh B) hepatic impairment: Reduce the starting dose by 50%.
Severe (Child-Pugh C) hepatic impairment: Avoid Deferasirox.

Back

Patients with baseline renal impairment:
For patients with a baseline serum creatinine less than 2 times the age appropriate upper limit of normal, initial dosing is the same as described for patients with a normal creatinine. Do not use Deferasirox in patients with serum creatinine greater than 2 times the upper limit of normal.
Dose modifications for increases in serum creatinine on deferasirox:
For serum creatinine increases while receiving Deferasirox, modify the dose as follows:
Transfusional iron overload:
Adults and adolescents (ages 16 and older):
- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within one week, and if still elevated by 33% or more, reduce the dose by 10 mg per kg.

Pediatric Patients (ages 2-15 years):
- Reduce the dose by 10 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

All Patients (regardless of age):
- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min.

Non-transfusion dependent thalassemia syndromes:
Adults and adolescents (ages 16 and older):
- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within one week, and if still elevated by 33% or more, interrupt therapy if the dose is 5 mg per kg, or reduce by 50% if the dose is 10 or 20 mg per kg.

Pediatric Patients (ages 10-15 years):
- Reduce the dose by 5 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

All Patients (regardless of age):
Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min .
Dose modifications based on concomitant medications:
UDP-glucuronosyltransferases (UGT) inducers:
Concomitant use of UGT inducers decreases Deferasirox systemic exposure. Avoid the concomitant use of potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) with Deferasirox. If you must administer Deferasirox with one of these agents, consider increasing the initial dose of Deferasirox by 50%, and monitor serum ferritin levels and clinical responses for further dose modification.
Bile acid sequestrants:
Concomitant use of bile acid sequestrants decreases Deferasirox systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Deferasirox. If you must administer Deferasirox with one of these agents, consider increasing the initial dose of Deferasirox by 50%, and monitor serum ferritin levels and clinical responses for further dose modification.

CONTRAINDICATIONS:
Deferasirox is contraindicated in patients with:
- Serum creatinine greater than 2 times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min .
- Poor performance status;
- High-risk myelodysplastic syndromes;
- Advanced malignancies;
- Platelet counts <50 x 10^9/L;
- Known hypersensitivity to Deferasirox or any component of Deferasirox .

WARNINGS AND PRECAUTIONS:
Renal toxicity, renal failure and proteinuria:
Deferasirox can cause acute renal failure, fatal in some patients and requiring dialysis in others. Measure serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (estimated by the Cockcroft-Gault method) before initiating therapy in all patients in order to establish a reliable pretreatment baseline. Monitor serum creatinine weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Monitor serum creatinine and/or creatinine clearance more frequently if creatinine levels are increasing. Dose reduction, interruption, or discontinuation based on increases in serum creatinine may be necessary. Deferasirox is contraindicated in patients with creatinine clearance less than 40 mL/minute or serum creatinine greater than 2 times the age appropriate upper limit of normal. Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with Deferasirox, most commonly in children and adolescents with β-thalassemia and serum ferritin levels <1500 mcg/L. Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) may occur., Deferasirox was temporarily withheld until the urine protein/creatinine ratio fell below 0.6 mg/mg. Monthly monitoring for proteinuria is recommended. The mechanism and clinical significance of the proteinuria are uncertain.
Hepatic toxicity and failure:
Deferasirox can cause hepatic injury, fatal in some patients. Hepatic toxicity appears to be more common in patients greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multi organ failure.
Measure transaminases (AST and ALT) and bilirubin in all patients before the initiation of treatment and every 2 weeks during the first month and at least monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.
Avoid the use of Deferasirox in patients with severe (Child-Pugh C) hepatic impairment. Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.
Gastrointestinal (gi) hemorrhage:
GI hemorrhage, including deaths, has been reported, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Non-fatal upper GI irritation, ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Deferasirox. Monitor for signs and symptoms of GI ulceration and hemorrhage during Deferasirox therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. The risk of gastrointestinal hemorrhage may be increased when administering Deferasirox in combination with drugs that have ulcerogenic or hemorrhagic potential, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants.
Bone marrow suppression:
Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events, have been reported in patients treated with Deferasirox. Pre-existing hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with Deferasirox in patients who develop cytopenias until the cause of the cytopenia has been determined. Deferasirox is contraindicated in patients with platelet counts below 50 x 10^9/L.
Increased risk of toxicity in the elderly:
Deferasirox has been associated with serious and fatal adverse reactions in the postmarketing setting, predominantly in elderly patients. Monitor elderly patients treated with Deferasirox more frequently for toxicity.
Hypersensitivity:
Deferasirox may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment . If reactions are severe, discontinue Deferasirox and institute appropriate medical intervention. Deferasirox is contraindicated in patients with known hypersensitivity to Deferasirox.
Skin rash:
Rashes may occur during Deferasirox treatment. For rashes of mild to moderate severity, Deferasirox may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with Deferasirox. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.
Erythema multiforme:
Erythema multiforme has been reported during Deferasirox therapy. If erythema multiforme is suspected, discontinue Deferasirox and evaluate.
Auditory and Ocular Abnormalities:
Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) were reported at a frequency of <1% with Deferasirox therapy in the clinical studies. Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting Deferasirox treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.
Overchelation:
For patients with transfusional iron overload, measure serum ferritin monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500 mcg/L , consider interrupting therapy with Deferasirox, since overchelation may increase Deferasirox toxicity. For patients with non-transfusion dependent thalassemia, measure LIC by liver biopsy or by using an FDA-cleared or approved method for monitoring patients receiving Deferasirox therapy every 6 months on treatment. Interrupt Deferasirox administration when the LIC is less than 3 mg Fe/g dw. Measure serum ferritin monthly, and if the serum ferritin falls below 300 mcg/L, interrupt Deferasirox and obtain a confirmatory LIC.

ADVERSE REACTIONS:
The following adverse reactions may occur.
- Renal Toxicity, Renal Failure and Proteinuria
- Hepatic Toxicity and Failure
- Gastrointestinal Hemorrhage
- Bone Marrow Suppression
- Skin Rash
- Auditory and Ocular Abnormalities
- Abdominal Pain
- Diarrhea
- Creatinine Increased
- Nausea
- Vomiting
- Rash

OVERDOSAGE:
In case of overdose, induce vomiting, employ gastric lavage and supportive therapy.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Take this medicine on an empty stomach.
- Disperse tablet in water before swallowing.
- Do not swallow or chew the whole tablet.
- Keep out of the reach of children.
- To be sold on prescription of a registered medical practitioner only.

PRESENTATION:

Dasirox Tablet 100 mg	:	Pack of 6 x 5 tablets.
Dasirox Tablet 250 mg	:	Pack of 5 x 6 tablets.
Dasirox Tablet 400 mg	:	Pack of 5 x 6 tablets.
Dasirox Tablet 500 mg	:	Pack of 5 x 6 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔ دوا کو خالی پیٹ استعمال کریں۔
گولی کو پانی میں حل کر کے پئیں۔ ثابت گولی نہ نگلیں اور نہ ہی چبائیں۔
بچوں کی پہنچ سے دور رکھیں۔ صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

2036-B
25012-0001-001-0000-0000