DEFERA
(Deferasirox)

250mg & 500mg Dispersible

Tablets

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

Renal Failure
Deferasirox can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.
Evaluate baseline renal function prior to starting or increasing deferasirox dosing in all patients. Deferasirox is contraindicated in adult and pediatric patients with eGFR less than 40 mL/min/1.73 m^2. Measure serum creatinine in duplicate prior to initiation of therapy. Monitor renal function at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, then at least monthly. Reduce the starting dose in patients with preexisting renal disease. During therapy, increase the frequency of monitoring and modify the dose for patients with an increased risk of renal impairment, including use of concomitant nephrotoxic drugs, and pediatric patients with volume depletion or over chelation.
Hepatic Failure
Deferasirox can cause hepatic injury including hepatic failure and death.
Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter.
Avoid use of deferasirox in patients with severe (Child-Pugh C) hepatic impairment and reduce the dose in patients with moderate (Child-Pugh B) hepatic impairment.
Gastrointestinal Hemorrhage
Deferasirox can cause gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts.
Monitor patients and discontinue deferasirox for suspected GI ulceration or hemorrhage.

COMPOSITION

Defera 250mg Tablets
Each dispersible tablet contains:
Deferasirox……. 250mg
(As per innovator's specifications)

Defera 500mg Tablets
Each dispersible tablet contains:
Deferasirox……. 500mg
(As per innovator's specifications)

THERAPEUTIC INDICATIONS

Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)
Deferasirox tablets for oral suspension are indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older**.**
Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes
Deferasirox tablets for oral suspension are indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) 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.
Limitations of Use
The safety and efficacy of deferasirox when administered with other iron chelation therapy 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 1,000 mcg/L.

Prior to starting therapy or increasing dose, evaluate:

- Serum ferritin level
- Baseline renal function:
    - Obtain serum creatinine in duplicate (due to variations in measurements) to establish accurate baseline
    - Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
    - Obtain urinalyses and serum electrolytes to evaluate renal tubular function
- Serum transaminases and bilirubin
- Baseline auditory and ophthalmic examinations

Initiating Therapy:
The recommended initial dose of deferasirox for patients 2 years of age and older with eGFR greater than 60 mL/min/1.73 m2 is 20 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
During Therapy:

- Monitor serum ferritin monthly and adjust the dose of deferasirox, if necessary, every 3 to 6 months based on serum ferritin trends.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- 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 2,500 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
- Adjust dose based on serum ferritin levels
    - If the serum ferritin falls below 1,000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the dose is greater than 25 mg/kg/day
    - If the serum ferritin falls below 500 mcg/L, interrupt deferasirox to minimize the risk of overchelation, and continue monthly monitoring
    - Evaluate the need for ongoing chelation therapy for patients whose conditions no longer require regular blood transfusions.
    - Use the minimum effective dose to maintain iron burden in the target range
- Monitor blood counts, liver function, renal function and ferritin monthly
- Interrupt deferasirox for pediatric patients who have acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Deferasirox therapy should only be considered when a patient with NTDT 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
- Serum ferritin level on at least 2 measurements 1-month apart
- Baseline renal function:
- Obtain serum creatinine in duplicate (due to variations in measurements) to establish accurate baseline
- Calculate eGFR. Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
- Obtain urinalyses and serum electrolytes to evaluate renal tubular function
- Serum transaminases and bilirubin
- Baseline auditory and ophthalmic examinations

Initiating Therapy:

- The recommended initial dose of deferasirox for patients with eGFR greater than 60 mL/min/1.73 m2 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 to assess the patient's response to therapy and to minimize the risk of overchelation. 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.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- 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 to 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, liver function, renal function and ferritin monthly
- Increase monitoring frequency for pediatric patients who have acute illness, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake. Consider dose interruption until oral intake and volume status are normal

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

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

Patients with Baseline Renal Impairment
Do not use deferasirox in adult or pediatric patients with eGFR less than 40 mL/min/1.73 m2
For patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2), reduce the starting dose by 50%
Exercise caution in pediatric patients with eGFR between 40 and 60 mL/min/1.73 m^2. If treatment is needed, use the minimum effective dose and monitor renal function frequently. Individualize dose titration based on improvement in renal injury

Dose Modifications for Decreases in Renal Function While on Deferasirox

Deferasirox is contraindicated in patients with eGFR less than 40 mL/min/1.73 m^2
For decreases in renal function while receiving deferasirox , modify the dose as follows:
Transfusional Iron Overload
Adults:

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, reduce the dose by 10 mg per kg.

Pediatric Patients (ages 2 years to 17 years):

- Reduce the dose by 10 mg/kg/day if eGFR decreases by greater than 33% below the average baseline measurement and repeat the eGFR within 1 week.
- Interrupt deferasirox for acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Avoid use of other nephrotoxic drugs.
- In the setting of decreased renal function, evaluate the risk benefit profile of continued deferasirox use. Use the minimum effective deferasirox dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic therapies until improvement of renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt deferasirox to prevent severe and irreversible renal injury.

All Patients (regardless of age):

- Discontinue therapy for eGFR less than 40 mL/min/1.73 m^2.

Non-Transfusion-Dependent Thalassemia Syndromes
Adults:

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 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 years to 17 years):

- Reduce the dose by 5 mg/kg/day if eGFR decreases by greater than 33% below the average baseline measurement and repeat the eGFR within 1 week.
- Increase monitoring frequency for pediatric patients who have acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake. Consider dose interruption until oral intake and volume status are normal. Avoid use of other nephrotoxic drugs.
- In the setting of decreased renal function, evaluate the risk benefit profile of continued deferasirox use. Use the minimum effective deferasirox dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic therapies until improvement of renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt deferasirox to prevent severe and irreversible renal injury.

All Patients (regardless of age):

- Discontinue therapy for eGFR less than 40 mL/min/1.73 m^2.

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 1 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 1 of these agents, consider increasing the initial dose of deferasirox by 50%, and monitor serum ferritin levels and clinical responses for further dose modification

Method of 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, resuspend any residue in a small volume of liquid and swallow. Do not take deferasirox with aluminum-containing antacid products

CONTRAINDICATIONS

Deferasirox is contraindicated in patients with:

- Estimated GFR less than 40 mL/min/1.73 m^2
- Poor performance status;
- High-risk myelodysplastic syndromes; *(this patient population was not studied and is not expected to benefit from chelation therapy)*
- *Advanced malignancies;*
- *Platelet counts less than 50 x 109/L;*
- *Known hypersensitivity to deferasirox or any component of deferasirox*

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Acute Kidney Injury, Including Acute Renal Failure Requiring Dialysis, and Renal Tubular Toxicity Including Fanconi Syndrome

Deferasirox is contraindicated in patients with eGFR less than 40 mL/min/1.73 m^2. Exercise caution in pediatric patients with eGFR between 40 and 60 mL/minute/1.73 m^2. If treatment is needed, use the minimum effective dose and monitor renal function frequently. Individualize dose titration based on improvement in renal injury. For patients with renal

impairment (eGFR 40 to 60 mL/min/1.73 m^2), reduce the starting dose by 50%

Deferasirox can cause acute kidney injury including renal failure requiring dialysis that has resulted in fatal outcomes. Based on postmarketing experience, most fatalities have occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, adult and pediatric deferasirox-treated patients with no preexisting renal disease experienced dose-dependent mild, non-progressive increases in serum creatinine and proteinuria. Preexisting renal disease and concomitant use of other nephrotoxic drugs may increase the risk of acute kidney injury in adult and pediatric patients. Acute illnesses associated with volume depletion and overchelation may increase the risk of acute kidney injury in pediatric patients. In pediatric patients, small decreases in eGFR can result in increases in deferasirox exposure, particularly in younger patients with body surface area typical of patients less than age 7 years. This can lead to a cycle of worsening renal function and further increases in deferasirox exposure, unless the dose is reduced or interrupted. Renal tubular toxicity, including acquired Fanconi syndrome, has been reported in patients treated with deferasirox, most commonly in pediatric patients with beta-thalassemia and serum ferritin levels less than 1,500 mcg/L

Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose. Use prediction equations validated for use in adult and pediatric patients to estimate GFR. Obtain serum electrolytes and urinalysis in all patients to evaluate renal tubular function

Monitor all patients for changes in eGFR and for renal tubular toxicity weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Dose reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated. Monitor serum ferritin monthly to evaluate for overchelation. Use the minimum dose to establish and maintain a low iron burden. Monitor renal function more frequently in patients with preexisting renal disease or decreased renal function. In pediatric patients, interrupt deferasirox during acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor renal function more frequently. Promptly correct fluid deficits to prevent renal injury. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal

Hepatic Toxicity and Failure

Deferasirox can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) discontinued deferasirox because of hepatic toxicity (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional 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. Acute liver injury and failure, including fatal outcomes, have occurred in pediatric deferasirox-treated patients. Liver failure occurred in association with acute kidney injury in pediatric patients at risk for overchelation during a volume depleting event. Interrupt deferasirox therapy when acute liver injury or acute kidney injury is suspected and during volume depletion. Monitor liver and renal function more frequently in pediatric patients who are receiving deferasirox in the 20 to 40 mg/kg/day range and when iron burden is approaching normal. Use the minimum effective dose to achieve and maintain a low iron burden

Measure transaminases [aspartate transaminase (AST) and alanine transaminase (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) Ulceration, Hemorrhage, and Perforation

GI hemorrhage, including deaths, has been reported in deferasirox-treated patients, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Nonfatal 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 reaction is suspected. The risk of GI hemorrhage may be increased when administering deferasirox in combination with drugs that have ulcerogenic or hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants. There have been reports of ulcers complicated with GI perforation (including fatal outcome).

Bone Marrow Suppression

Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events, have been reported in patients treated with deferasirox. Preexisting hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with deferasirox in patients who develop cytopenia until the cause of the cytopenia has been determined. Deferasirox is contraindicated in patients with platelet counts below 50 x 109/L.

Age-Related Risk of Toxicity

Elderly Patients

Deferasirox has been associated with serious and fatal adverse reactions in the post marketing setting among adults, predominantly in elderly patients. Monitor elderly patients treated with deferasirox more frequently for toxicity.

Pediatric Patients

Deferasirox has been associated with serious and fatal adverse reactions in pediatric patients in the post marketing setting. These events were frequently associated with volume depletion or with continued deferasirox doses in the 20 to 40 mg/kg/day range when body iron burden was approaching or in the normal range. Interrupt deferasirox in patients with volume depletion, and resume deferasirox when renal function and fluid volume have normalized. Monitor liver and renal function more frequently during volume depletion and in patients receiving deferasirox in the 20 to 40 mg/kg/day range when iron burden is approaching the normal range. Use the minimum effective dose to achieve and maintain a low iron burden.

Overchelation

For patients with transfusional iron overload, measure serum ferritin monthly to assess the patient's response to therapy and minimize the risk of overchelation. An analysis of pediatric patients treated with deferasirox in pooled clinical trials (n = 158) found a higher rate of renal adverse reactions among patients receiving doses greater than 25 mg/kg/day while their serum ferritin values were less than 1,000 mcg/L. Consider dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels during these periods. Use the minimum effective dose to maintain a low-iron burden.

If the serum ferritin falls below 1,000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the dose is greater than 25 mg/kg/day . If the serum ferritin falls below 500 mcg/L, interrupt therapy with deferasirox and continue monthly monitoring. Evaluate the need for ongoing chelation for patients whose conditions do not require regular blood transfusions. Use the minimum effective dose to maintain iron burden in the target range. Continued administration of deferasirox in the 20 to 40 mg/kg/day range when the body iron burden is approaching or within the normal range has resulted in life-threatening adverse reactions.

For patients with NTDT, 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.

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 products and should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox products due to the risk of anaphylactic shock.

Severe Skin Reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal have been reported during deferasirox therapy. Cases of erythema multiforme have been observed. Advise patients of the signs and symptoms of severe skin reactions, and closely monitor. If any severe skin reactions are suspected, discontinue deferasirox immediately and do not reintroduce deferasirox therapy.

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 after resolution of the rash.

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 less than 1% with deferasirox therapy in the clinical studies. The frequency of auditory adverse reactions was increased among pediatric patients who received deferasirox doses greater than 25 mg/kg/day when serum ferritin was less than 1,000 mcg/L

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.

DRUG INTERACTIONS

Aluminum-Containing Antacid Preparations

The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, do not take 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 coadministered. 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 coadministered. 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 coadministered 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 coadministered. 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 coadminister theophylline with deferasirox. Closely monitor patients for signs of exposure related toxicity when deferasirox is coadministered 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 coadminister 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 coadminister these agents together, consider increasing the initial dose of deferasirox.

Busulfan

Increased exposure of busulfan was observed with concomitant use with deferasirox. Monitor plasma concentrations of busulfan when Co-administered with deferasirox to allow dose adjustment of busulfan as needed.

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 Deferasirox is not used during pregnancy unless clearly necessary.

Deferasirox 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 Deferasirox.

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 Deferasirox 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

Deferasirox has minor influence on the ability to drive and use machines. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machines

ADVERSE DRUG REACTIONS

Summary of the safety profile

The most frequent reactions reported during chronic treatment in clinical studies conducted with deferasirox dispersible tablets in adult and pediatric patients include gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash. 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.

During clinical studies dose-dependent increases in serum creatinine occurred in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been observed in both pediatric and adult patients with beta-thalassemia and iron overload during the first year of treatment, but there is evidence that this does not decrease further in subsequent years of treatment. Elevations of liver transaminases have been reported. Safety monitoring schedules for renal and liver parameters are recommended. Auditory (decreased hearing) and ocular

(lens opacities) disturbances are uncommon, and yearly examinations are also recommended.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of Deferasirox.

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 seriousness.

Blood and lymphatic system disorders	
Not known:	Pancytopenia[1], thrombocytopenia[1], anemia aggravated[1], neutropenia[1]
Immune system disorders	
Not known:	Hypersensitivity reactions (including anaphylactic reactions and angioedema)[1]
Metabolism and nutrition disorders	
Not known:	Metabolic acidosis[1]
Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Cataract, maculopathy
Rare:	Optic neuritis
Ear and labyrinth disorders	
Uncommon:	Deafness
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Laryngeal 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:	Esophagitis
Not known:	Gastrointestinal perforation[1], acute pancreatitis[1]
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Not known:	Hepatic failure[1, 2]
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Rare:	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Not known:	Stevens-Johnson syndrome[1], hypersensitivity vasculitis[1], urticaria[1], erythema multiforme[1], alopecia[1], toxic epidermal necrolysis (TEN)[1]
Renal and urinary disorders	
Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Renal tubular disorder[2] (acquired Fanconi syndrome), glycosuria
Not known:	Acute renal failure[1, 2], tubulointerstitial nephritis[1], nephrolithiasis[1], renal tubular necrosis[1]
General disorders and administration site conditions	
Uncommon:	Pyrexia, oedema, fatigue

[1] Adverse reactions reported during post-marketing 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.

[2] Severe forms associated with changes in consciousness in the context of hyperammonemic encephalopathy have been reported.

Description of selected adverse reactions

Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During post-marketing experience, hepatic failure, sometimes fatal, has been reported with deferasirox. There have been post-marketing reports of metabolic acidosis. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Cases of serious acute pancreatitis were observed without documented underlying biliary conditions. As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.

Creatinine clearance in transfusional iron overload

In a retrospective meta-analysis of 2,102 adult and pediatric beta-thalassemia patients with transfusional iron overload treated with deferasirox dispersible tablets in two randomized and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935) and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in pediatric patients was observed during the first year of treatment. In 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed.

Clinical study in patients with non-transfusion-dependent thalassemia syndromes

In a 1-year study in patients with non-transfusion-dependent thalassemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day),

diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8% of patients, respectively. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal were reported in 1.8% of patients.

Pediatric population

In two clinical studies, growth and sexual development of pediatric patients treated with deferasirox for up to 5 years were not affected.

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-thalassemia treated with deferasirox. In post-marketing reports, a high proportion of cases of metabolic acidosis occurred in children in the context of Fanconi syndrome.

Acute pancreatitis has been reported, particularly in children and adolescents.

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 at pv@searlecompany.com

OVERDOSE

Early signs 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 which resolved after treatment.

There is no specific antidote for deferasirox. Standard procedures for management of overdose may be indicated as well as symptomatic treatment, as medically appropriate

PHARMACOLOGICAL PROPERTIES

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.

Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study showed that deferasirox (10, 20, and 40 mg per kg per day) was able to induce a mean net iron excretion (0.119, 0.329, and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1 to 0.5 mg per kg per day). Iron excretion was predominantly fecal.

An analysis of pooled pediatric clinical trial data found a statistically significant relationship between exposure and the probability of renal toxicity (increase in serum creatinine and urinary protein), resulting in a decrease in renal function. Decreases in renal function resulted in an increase in deferasirox exposure, which may increase the probability of renal toxicity.

Cardiac Electrophysiology

At the maximum approved recommended dose, deferasirox does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics

Absorption

Deferasirox is absorbed following oral administration with median times to maximum plasma concentration (Tmax) of about 1.5 to 4 hours. The Cmax and area under the curve (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 to 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. Deconjugation of glucuronidatess 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-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy volunteer study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) by interfering with the enterohepatic recycling of deferasirox.

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 (t1/2) ranged from 8 to 16 hours following oral administration.

Drug Interactions

Midazolam: In healthy volunteers, the concomitant administration of deferasirox and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam peak concentration by 23% and exposure by 17%. In the clinical setting, this effect may be more pronounced. The study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox.

Repaglinide: In a healthy volunteer study, the concomitant administration of deferasirox (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold of control and an increase in Cmax of 62%.

Theophylline: In a healthy volunteer study, the concomitant administration of deferasirox (repeated dose of 30 mg per kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an approximate doubling of the theophylline AUC and elimination half-life. The single dose Cmax was not affected, but an increase in theophylline Cmax is expected to occur with chronic dosing.

Rifampicin: In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg per kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (600 mg/day for 9 days) resulted in a decrease of deferasirox systemic exposure (AUC) by 44%.

Cholestyramine: The concomitant use of deferasirox with bile acid sequestrants may result in a decrease in deferasirox efficacy. In healthy volunteers, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

Busulfan: Concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC).

In vitro Studies:

- Cytochrome P450 Enzymes: Deferasirox inhibits human CYP3A4, CYP2C8, CYP1A2, CYP2A6, CYP2D6, and CYP2C19 *in vitro*.
- Transporter Systems: The addition of cyclosporin A (PgP/MRP1/MRP2 inhibitor) or verapamil (PgP/MRP1 inhibitor) did not influence ICL670 permeability *in vitro*.

Pharmacokinetics in Specific Populations

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children less than 6 years of age, systemic exposure was about 50% lower than in adults.

Geriatric: The pharmacokinetics of deferasirox have not been studied in elderly patients (65 years of age or older).

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

Renal Impairment: Compared to patients with MDS and eGFR greater than 60 mL/min/1.73 m2, patients with MDS and eGFR 40 to 60 mL/min/1.73 m2 (n = 34) had approximately 50% higher mean deferasirox trough plasma concentrations.

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 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

Transfusional Iron Overload

The primary efficacy study, Study 1 (NCT00061750), was a multicenter, open-label, randomized, active-comparator control study to compare deferasirox and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients greater than or equal to 2 years of age were randomized in a 1:1 ratio to receive either oral deferasirox at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous deferoxamine at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2 to 3, greater than 3 to 7, greater than 7 to 14, and greater than 14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values less than 7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of greater than or equal to 3 mg Fe/g dry weight for baseline values greater than or equal to 10 mg Fe/g dry weight, reduction of baseline values between 7 and less than 10 to less than 7 mg Fe/g dry weight, or maintenance or reduction for baseline values less than 7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with deferasirox and 290 with deferoxamine. The mean age was 17.1 years (range, 2 to 53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (deferasirox n = 276; deferoxamine n = 277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse reaction. The percentage of patients achieving the primary endpoint was 52.9% for deferasirox and 66.4% for deferoxamine. The relative efficacy of deferasirox to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with deferasirox and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with deferasirox doses of 20 to 30 mg per kg per day. Deferasirox doses below 20 mg per kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg per kg per day is recommended.

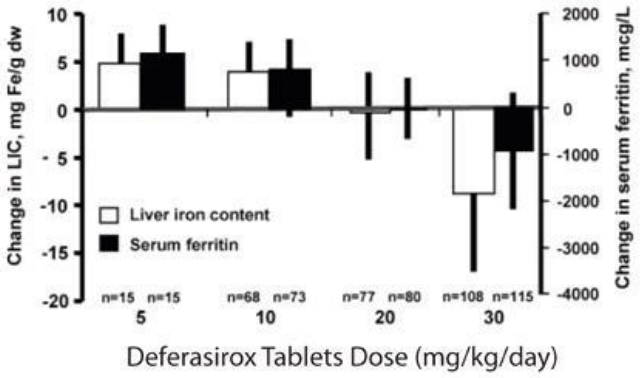

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox (5 to 30 mg per kg per day) in Study 1

Study 2 (NCT00061763) was an open-label, noncomparative trial of efficacy and safety of deferasirox given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg per kg per day of deferasirox based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n = 47; Diamond-Blackfan syndrome, n = 30; other, n = 22). Nineteen percent (19%) of patients were less than 16 years of age and 16% were greater than 65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 (NCT00067080) was a multicenter, open-label, randomized trial of the safety and efficacy of deferasirox relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to deferasirox at doses of 5, 10, 20, or 30 mg per kg per day or subcutaneous deferoxamine at doses of 20 to 60 mg per kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with deferasirox and 63 with deferoxamine. Forty-four percent (44%) of patients were less than 16 years of age and 91% were black. At end of study, the mean change in LIC (as measured by magnetic susceptometry by a superconducting quantum interference device) in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox (n = 113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n = 54).

One-hundred five (105) patients with thalassemia major and cardiac iron overload were enrolled in a study assessing the change in cardiac magnetic resonance imaging (MRI) T2* value (measured in milliseconds, ms) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to less than 20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of deferasirox therapy increased from 11.98 ms at baseline to 17.12 ms at 3 years. Cardiac T2* values improved in patients with severe cardiac iron overload (less than 10 ms) and in those with mild to moderate cardiac iron overload (greater than or equal to 10 to less than 20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven (627) patients with MDS were enrolled across 5 uncontrolled trials. Two hundred thirty-nine (239) of the 627 patients were enrolled in trials that limited enrollment to patients with IPSS Low or Intermediate 1 risk MDS, and the remaining 388 patients were enrolled in trials that did not specify MDS risk stratification but required a life expectancy of greater than 1 year. Planned duration of treatment in these trials ranged from 1 year (365 patients) to 5 years (47 patients). These trials evaluated the effects of deferasirox therapy on parameters of iron overload, including LIC (125 patients) and serum ferritin (627 patients). The percent of patients completing planned duration of treatment was 51% in the largest 1-year study, 52% in the 3-year study and 22% in the 5-year study. The major causes for treatment discontinuation were withdrawal of consent, adverse reaction, and death. Over 1 year of follow-up across these pooled studies, mean change in serum ferritin was -332.8 (± 2615.59) mcg/L (n = 593) and mean change in LIC was -5.9 (± 8.32) mg Fe/g dw (n = 68). Results of these pooled studies in 627 patients with MDS suggest a progressive decrease in serum ferritin and LIC beyond 1 year in those patients who are able to continue deferasirox.

Non-Transfusion Dependent Thalassemia

Study 5 (NCT00873041) was a randomized, double-blind, placebo-controlled trial of treatment with deferasirox for patients 10 years of age or older with NTDT syndromes and iron overload. Eligible patients had an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin exceeding 300 mcg/L at screening (2 consecutive values at least 14 days apart from each other). A total of 166 patients were randomized, 55 to the deferasirox 5 mg/kg/day dose group, 55 to the deferasirox 10 mg/kg/day dose group, and 56 to placebo (28 to each matching placebo group). Doses could be increased after 6 months if the LIC exceeded 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The patients enrolled included 89 males and 77 females. The underlying disease was beta-thalassemia intermedia in 95 (57%) patients, HbE beta-thalassemia in 49 (30%) patients, and alpha-thalassemia in 22 (13%) patients. There were 17 pediatric patients in the study. Caucasians comprised 57% of the study population and Asians comprised 42%. The median baseline LIC (range) for all patients was 12.1 (2.6 to 49.1) mg Fe/g dw. Follow-up was for 1 year. The primary efficacy endpoint of change in LIC from baseline to Week 52 was statistically significant in favor of both deferasirox dose groups compared with placebo ($p \leq 0.001$) (Table 5). Furthermore, a statistically significant dose effect of deferasirox was observed in favor of the 10 mg/kg/day dose group (10 versus 5 mg/kg/day, $p = 0.009$). In a descriptive analysis, the target LIC (less than 5 mg Fe/g dw) was reached by 15 (27%) of 55 patients in the 10 mg/kg/day arm, 8 (15%) of 55 patients in the 5 mg/kg/day arm and 2 (4%) of 56 patients in the combined placebo groups.

Study 6 (NCT00873041) was an open-label trial of deferasirox for the treatment of patients previously enrolled on Study 5, including cross-over to active treatment for those previously treated with placebo. The starting dose of deferasirox in Study 6 was assigned based on the patient's LIC at completion of Study 5, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3 to 15 mg Fe/g dw, and observation if the LIC was less than 3 mg Fe/g dw. Patients could continue on 5 mg/kg/day if they had previously exhibited at least a 30% reduction in LIC. Doses could be increased to a maximum of 20 mg/kg/day after 6 months if the LIC was more than 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The primary efficacy endpoint in Study 6 was the proportion of patients achieving an LIC less than 5 mg Fe/g dw. A total of 133 patients were enrolled. Twenty patients began Study 6 with an LIC less than 5 mg Fe/g dw. Of the 113 patients with a baseline LIC of at least 5 mg Fe/g dw in Study 6, the target LIC (less than 5 mg Fe/g dw) was reached by 39 patients (35%). The responders included 4 (10%) of 39 patients treated at 20 mg/kg/day for a baseline LIC exceeding 15 mg Fe/g dw, and 31 (51%) of 61 patients treated at 10 mg/kg/day for a baseline LIC between 5 and 15 mg Fe/g dw. The absolute change in LIC at Week 52 by starting dose is shown in Table below.

Deferasirox Tablets for Oral Suspension Starting Dose

Table: Absolute Change in LIC at Week 52 in Patients with NTDT

	Placebo	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Study 5[b]				
Number of Patients	n = 54	n = 51	n = 54	-
Mean LIC at Baseline (mg Fe/g dw)	16.1	13.4	14.4	-
Mean Change (mg Fe/g dw)	+0.4	-2.0	-3.8	-
(95% Confidence Interval)	(-0.6, +1.3)	(-2.9, -1.0)	(-4.8, -2.9)	-
Study 6				
Number of Patients	-	n = 8	n = 77	n = 43
Mean LIC at Baseline (mg Fe/g dw)	-	5.6	8.8	23.5
Mean Change (mg Fe/g dw)	-	-1.5	-2.8	-9.1
(95% Confidence Interval)	-	(-3.7, +0.7)	(-3.4, -2.2)	(-11.0, -7.3)

Abbreviation: LIC, liver iron concentration; NTDT, non-transfusion-dependent thalassemia.

[a] Randomized dose in Study 5 or assigned starting dose in Study 6.

[b] Least square mean change for Study 5.

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg per kg per day (0.48 times the MRHD on an mg/m2 basis). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg per kg per day (0.81 times the MRHD on a mg/m2 basis) in males and 300 mg per kg per day (1.21 times the MRHD on a mg/m2 basis) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg per kg per day (0.6 times the MRHD on a mg/m2 basis) was found to have no adverse effect on fertility and reproductive performance of male and female rat.

PRESENTATION

Defera 250mg Dispersible Tablets: 28 tablets are available in alu alu blister packaging.

Defera 500mg Dispersible Tablets: 28 tablets are available in alu alu blister packaging.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Defera 250mg Tablets : 100421

Defera 500mg Tablets : 100422

Manufacturing licence Number : 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited.

F-319, S.I.T.E., Karachi-Pakistan.

Marketed by:

IBL HealthCare Limited,

One IBL Centre, 2nd Floor, Plot # 1,

Block 7 & 8, D.M.C.H.S, Tipu Sultan Road

Off Shahra-e-Faisal, Karachi - Pakistan.

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