Osveral® (Deferasirox)

Category:

Iron chelating agent

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 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.
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 glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3.
CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No evidence for induction or inhibition of enzymes at therapeutic doses has been observed.
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 to 16 hours following oral administration.

Mechanism of action:

Deferasirox is an orally active chelator that is selective for iron (as Fe^{3+}). 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.

Indications:

Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

Administration and Dosage:

It is recommended that therapy with Osveral® (deferasirox) be started when a patient has evidence of chronic iron overload, such as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40-kg patient) and a serum ferritin consistently >1000 mcg/L.
Starting Dose: The recommended initial daily dose of deferasirox is 20 mg/kg body weight.
Maintenance: After commencing initial therapy, it is recommended that serum ferritin be monitored every month and the dose of deferasirox adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 or 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with deferasirox. Doses of deferasirox should not exceed 30 mg/kg per day since there is limited experience with doses above this level.
Deferasirox should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Tablets should not be chewed or swallowed whole. Deferasirox should not be taken with aluminum-containing antacid products. Doses (mg/kg per day) should be calculated to the nearest whole tablet. Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of <1 g should be dispersed in 3.5 ounces of liquid and doses of ≥1 g in 7.0 ounces of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed.

Contraindications:

Use of deferasirox is contraindicated in patients with hypersensitivity to deferasirox or to any other component of Osveral®.

Precautions:

Skin 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, deferasirox may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.
Serum creatinine should be assessed in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Serum creatinine should be monitored monthly thereafter. Patients with additional renal risk factors should be monitored weekly during the first month after initiation or modification of therapy, and monitored monthly thereafter.
Liver function tests should be monitored monthly during deferasirox treatment and dose modifications considered for severe or persistent elevations.
Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox.

Pregnancy and breast feeding:

Pregnancy: Category B
Lactation: It is not known whether deferasirox is excreted in human milk. Deferasirox and its metabolites were excreted in breast milk of rats following a 10 mg/kg dose (about 0.08 times the recommended human oral dose based on body surface area). Because many drugs are excreted in human milk, caution should be exercised when deferasirox is administered to a nursing woman.

Side effects:

diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, cough, and increases in serum creatinine
(Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.)

Drug Interactions:

-Although deferasirox has a lower affinity for aluminum than for iron, deferasirox should not be taken with aluminum-containing antacid preparations.
-Interaction with Agents Metabolized by CYP450
-Interaction with Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism (rifampicin, phenytoin, phenobarbital, ritonavir)
-Interaction with Cholestyramine
-Deferasirox should not be combined with other iron chelator therapies.
-The bioavailability (AUC) of deferasirox was variably increased when taken with a meal. Deferasirox should be taken on an empty stomach 30 minutes before eating. (Deferasirox tablets for oral suspension can be dispersed in water, orange juice, or apple juice.)

Packaging:

Osveral® is available as 125, 250 and 500 mg dispersible tablets in box of 84 tablets.

Storage:

- Keep in the box, Store below 30 °C
- Protect from moisture and light
- Keep out of the reach of children