Deferiprone (Ferriprox Tablets)

**Manufacturer:** ApoPharma USA, Inc., Rockville, Md., a division of Apotex, Toronto, Canada

**Indication:** Deferiprone was approved under the FDA’s accelerated approval program for the treatment of transfusional iron overload in patients with thalassemia major when therapy with deferoxamine mesylate (Desferal, Novartis) is contraindicated or inadequate.

**Drug Class:** Deferiprone has an affinity for ferric ion. The tablets contain 500 mg of deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one). This synthetic, orally active, iron-chelating agent binds with ferric ions to form neutral 3:1 (deferiprone/iron) complexes that are stable over a wide range of pH values. Deferiprone has a higher binding affinity for iron than for other metals such as copper, aluminum, and zinc.

**Uniqueness of Drug:** Frequent blood transfusions are needed for patients with thalassemia, a genetic blood disorder that causes anemia. With repeated transfusions, the transfused red blood cells (RBCs) carry iron. However, the body does not have a natural way of removing excess iron, which accumulates. Over time, the excess iron can damage the heart and liver. Deferiprone binds to iron in the body to form a compound that can be eliminated, mainly in the urine and, to a lesser extent, in feces. This helps to correct the iron overload and to prevent tissue damage.

**Boxed Warning:**

**Neutropenia and Agranulocytosis.** Deferiprone has been shown to cause neutropenia, including agranulocytosis, which is characterized by a sudden drop in lymphocyte production. The patient’s absolute neutrophil count (ANC) should be monitored every week. In clinical trials, weekly monitoring of the ANC was effective in identifying cases of neutropenia and agranulocytosis, which resolved after therapy was withdrawn. If an infection develops during deferiprone therapy, treatment should be interrupted and the ANC should be monitored more frequently. Patients should be advised to inform their physicians immediately if any symptoms suggesting infection occur, such as fever, a sore throat, and flu-like symptoms.

**Warnings:**

**Agranulocytosis and neutropenia.** Fatal agranulocytosis has been reported with deferiprone use. Deferiprone can also cause neutropenia, which may foreshadow agranulocytosis. The ANC should be measured before deferiprone therapy is initiated, and it should be monitored weekly during therapy. If neutropenia develops (ANC below 1.5 × 10^9/L), treatment should be interrupted. If infection develops, therapy should be interrupted and the ANC should be monitored more frequently. Patients should be advised to interrupt therapy immediately and report any symptoms indicative of infection to their physician.

In pooled clinical trials, the incidence of agranulocytosis was 1.7% in treated patients. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone, but in some cases, agranulocytosis has led to death. A plan should be implemented to monitor and manage agranulocytosis and neutropenia before deferiprone therapy begins.

**Neutropenia.** If the ANC is between 1.5 × 10^9/L and 0.5 × 10^9/L, patients should be instructed to discontinue deferiprone and all other medications that have a potential to cause neutropenia. The clinician should obtain a complete blood cell (CBC) count, including a white blood cell (WBC) count, corrected for the presence of nucleated RBCs; an ANC; and a platelet count each day until recovery, indicated by an ANC of 1.5 × 10^9/L or greater.

**Agranulocytosis.** If the ANC is below 0.5 × 10^9/L, hospitalization or other management should be considered if clinically appropriate. Deferiprone treatment should not be resumed unless the potential benefits outweigh the risks. If neutropenia has developed, patients should not be re-challenged with deferiprone unless the potential benefits outweigh the risks.

**Cardiac QT syndrome.** No thorough QT studies have been conducted with deferiprone. One patient with a history of QT interval prolongation experienced torsades des pointes during treatment. Deferiprone should be administered with caution to patients who have an increased risk of a prolonged QT interval, such as those with congestive heart failure, bradycardia, cardiac hypertrophy, hypokalemia, or hypomagnesemia as well as those using a diuretic. Patients who experience symptoms suggestive of a cardiac arrhythmia (palpitations, dizziness, light-headedness, syncope, or seizures) are advised to seek medical attention immediately.

**Embryofetal toxicity.** In view of reports of genotoxicity and developmental toxicity in animal studies, deferiprone is likely to cause fetal harm when it is given to pregnant women. In animal studies, administration of deferiprone during organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. If deferiprone is used during pregnancy or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus. Women of reproductive age should be advised to avoid pregnancy if they are taking deferiprone.

**Laboratory Tests:**

**Serum liver enzymes.** In clinical studies, elevated levels of alanine transaminase (ALT) occurred in 7.5% of 642 subjects receiving deferiprone. Four deferiprone subjects (0.62%) discontinued the drug as a result of elevated serum ALT levels, and one patient (0.16%) stopped treatment because of elevations of both ALT and aspartate transaminase (AST). Serum ALT values should be monitored monthly during therapy with
Deferiprone is classified as a Pregnancy Category C drug. Interruption of therapy should be considered if there is a persistent increase in serum transaminase levels.

**Plasma zinc:** Decreased plasma zinc levels have been observed in patients receiving deferiprone therapy. Zinc levels should be monitored and supplemented if a deficiency is noted.

**Nonclinical Toxicology:**

**Carcinogenesis, mutagenesis, and fertility impairment.** Carcinogenicity studies have not been conducted with deferiprone; however, in view of the genotoxicity results and the findings of mammary hyperplasia and mammary tumors in rats treated with deferiprone in the 52-week toxicity study, tumor formation in carcinogenicity studies must be regarded as likely.

Results of an *in vitro* murine lymphoma assay were positive for the disease with deferiprone administration. In an *in vitro* chromosomal aberration test, deferiprone was clastogenic (disruptive to chromosomes). Given orally or intraperitoneally, deferiprone was also clastogenic in a bone marrow micronucleus assay in non–iron-loaded mice. The findings of a micronucleus test to detect genetic damage were also positive when mice were pre-treated with iron dextran and were subsequently treated with deferiprone. Deferiprone was not mutagenic in the Ames bacterial reverse mutation assay.

Sperm counts, motility, and morphology were unaffected in rats that were treated with deferiprone. No effects were observed on male or female fertility or reproductive function with the highest dose, which was 25% of the maximum recommended human dose based on body surface area.

**Pregnancy.** Deferiprone is classified as a Pregnancy Category D drug.

**Dosage and Administration:** The recommended initial dosage of deferiprone is 25 mg/kg orally three times per day, for a total of 75 mg/kg per day. The maximum dosage is 33 mg/kg three times per day, for a total of 99 mg/kg/day. Dosage adjustments up to 33 mg/kg three times per day should be tailored to the individual patient’s response and therapeutic goals of maintaining or reducing the body’s iron burden. The maximum recommended total daily dose is 99 mg/kg per day. Prescribers should round the dose to the nearest 250 mg (equivalent to a half-tablet).

Serum ferritin levels should be monitored every 2 to 3 months to assess the effects of deferiprone on body iron stores. If these concentrations fall consistently below 500 mcg/L, temporary interruption of therapy should be considered.

**Commentary:** Deferiprone, approved by the FDA in October, is an orally active, iron-chelating drug used in cases of transfusional iron overload. It was designed and developed primarily for patients with thalassemia. Thalassemia is endemic in Mediterranean regions, Middle East, and Southeast Asia, but it is considered an orphan disease in Europe and North America. Deferiprone is used to treat several other conditions involving iron or other metal imbalances and may have wider clinical applications.

At a dosage of 50 to 120 mg/kg per day, deferiprone appears to be effective in achieving a negative iron balance. Depending mainly on the patient’s iron load and the dose, the drug increases urinary iron excretion. It decreases serum ferritin levels and reduces the liver and heart iron content in most patients with iron overload from chronic transfusions of doses above 80 mg/kg per day. Deferiprone is metabolized to a gluconide conjugate and eliminated via the urine in the metabolized and in a nonmetabolized form. Elimination is usually in a 3:1 ratio of deferiprone/iron complex, which gives the characteristic red color to the urine.

Maximal serum concentrations of deferiprone are observed within 1 hour after oral administration, and the drug is cleared from blood within 6 hours. All adverse drug effects are considered reversible, controllable, and manageable. Discontinuation of deferiprone is recommended if agranulocytosis occurs.

The drug’s therapeutic index is similar to that of subcutaneous (SQ) deferoxamine (Desferal), but deferiprone is more effective removing iron from the heart, the target organ of iron toxicity in iron-loaded patients with thalassemia; deferiprone is also less expensive to produce than deferoxamine. A combination of deferoxamine and deferiprone has been used in patients who have been unable to comply with SQ deferoxamine, who have experienced toxicity, or who were not able to eliminate sufficient amounts of iron with the use of either drug alone. New oral iron-chelating drugs are being developed; however, even if they prove successful, they will probably be more expensive than deferiprone and are not likely to become available in the next 5 to 8 years.

**Sources:** www.fda.gov; www.rxlist.com/Ferriprox-drug.htm; www.ncbi.nlm.nih.gov/pubmed/12825969

**Ezogabine (Potiga Tablets)**

**Manufacturer:** Valeant, Durham, N.C./GlaxoSmithKline, Research Triangle Park, N.C.

**Indication:** Ezogabine is used as an adjunctive therapy for partial-onset seizures in patients 18 years of age and older.

**Drug Class:** The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester. The empirical formula is C<sub>19</sub>H<sub>16</sub>F<sub>1</sub>N<sub>3</sub>O<sub>3</sub>, and the molecular weight is 303.3.

**Uniqueness of Drug:** Ezogabine, a first-in-class activator of voltage-gated potassium channels in the brain, has been developed for the treatment of epilepsy. The mechanism of action is unknown, but the medication may act as an anticonvulsant by reducing excitability via the stabilization of neuronal potassium channels in an “open” position.

**Warnings and Precautions:**

**Urinary retention.** In placebo-controlled clinical trials, ezogabine therapy resulted in urinary retention, generally within the first 6 months of treatment; however, this effect was also observed later. Hydronephrosis occurred in two patients. In one of the patients, associated renal function impairment resolved upon discontinuation of treatment. Hydronephrosis was not reported in patients who received placebo.

In the trials, urinary retention, urinary hesitation, and dysuria were reported in 0.9%, 2.2%, and 2.3% of ezogabine-treated patients, respectively, and in 0.5%, 0.9%, and 0.7% of placebo patients, respectively. Because of the increased risk of urinary retention on ezogabine, urological symptoms should be carefully monitored.

**Neuropsychiatric symptoms.** In placebo-controlled epilepsy trials, confusion, psychotic symptoms, and hallucinations were reported more frequently in patients treated with ezogabine than in those treated with placebo. Discontinuations resulting from these reactions were more common in the drug-treated
group. These effects were dose-related and generally appeared within the first 8 weeks of treatment. Half of the patients who discontinued ezogabine because of hallucinations or psychosis required hospitalization. Approximately two-thirds of these patients with psychosis had no previous psychiatric history. Somnolence was reported in 22% of patients who were treated with ezogabine. Most of these adverse reactions were mild to moderate in intensity and occurred during the titration phase. For those patients who persisted with therapy, dizziness and somnolence diminished with continued treatment.

**QT interval prolongation.** In a study of cardiac conduction, ezogabine produced a mean prolonged QT interval of 7.7 msec in healthy volunteers when the dose was titrated to 400 mg three times daily. The QT-prolonging effect occurred within 3 hours. The QT interval should be monitored when ezogabine is prescribed with medications that are known to increase the QT interval and in patients with a known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia.

**Suicidal behavior and ideation.** Antiepileptic drugs, including ezogabine, have been found to increase the risk of suicidal thoughts or behavior. Patients who are being treated with an antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

**Withdrawal seizures.** As with all antiepileptic agents, ezogabine therapy should be withdrawn gradually, when possible, to minimize the potential of an increased frequency of seizures. The dosage should be reduced over a period of at least 3 weeks unless safety concerns warrant an abrupt withdrawal.

**Adverse Events:** Adverse drug events associated with ezogabine in clinical trials included dizziness, fatigue, confusion, vertigo, tremor, coordination problems, double vision, difficulty paying attention, memory impairment, and loss of strength.

**Dosage and Administration:** Ezogabine is available as 50-mg, 200-mg, 300-mg, and 400-mg film-coated, immediate-release oral tablets. It should be given in three equally divided doses daily, with or without food. The tablets should be swallowed whole. If therapy is discontinued, the dosage should be gradually reduced over a period of at least 3 weeks unless the drug must be withdrawn abruptly because of safety concerns.

**Commentary:** About one-third of patients with epilepsy do not achieve satisfactory seizure control with their current treatment. Ezogabine may be valuable in providing an alternative therapy for the treatment of partial seizures.

Although the drug was approved in mid-2011, it is not yet available. The FDA has recommended that ezogabine be classified as a controlled substance. The final classification is still under review by the Drug Enforcement Administration. It is anticipated that ezogabine might be available in pharmacies in the U.S. by the end of the year.

The drug’s approval was based on data from three placebo-controlled clinical studies involving 1,239 patients. A Risk Evaluation and Mitigation Strategy (REMS) program is required for ezogabine because of the potential for urinary retention and symptoms of acute urinary retention.

**Sources:** www.fda.gov; www.us.gsk.com; www.rxlist.com/potiga-drug.htm