Drug Use Research & Management Program
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Month/Year of Review: June 2012
New Drug: Deferiprone
Brand Name: Ferriprox®
Dossier: Yes

End date of literature search: March 5, 2012
Manufacturer: ApoPharma
Comparator Therapies: Deferasirox (PO) and deferoxamine (IV)

FDA Approved Indications:
Deferiprone is indicated for "the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate." Safety and effectiveness have not been established in other chronic anemias.

Research Questions:
1. How does deferiprone compare to other iron chelation therapy—deferoxamine and deferasirox—in the treatment of iron overload in patients with thalassemia syndromes?
2. Is deferiprone safer than deferoxamine or deferasirox?
3. Does deferiprone or the iron chelators reduce morbidity and mortality associated with iron overload in thalassemia?

Conclusions:
Significant morbidity and mortality are associated with iron overload in patients with thalassemia syndromes. Presently, deferiprone represents the only option for patients for whom deferoxamine and deferasirox are contraindicated or prove to be inadequate in reducing iron burden. There is insufficient evidence to compare the efficacy of deferiprone with the other oral agent, deferasirox.

There is insufficient evidence to determine whether deferiprone is more effective than currently available therapy. Italian guidelines indicate there is no strong evidence deferiprone in monotherapy or in combination with deferoxamine is superior to deferoxamine alone.[1,2] Accordingly, the FDA has approved deferiprone as second-line therapy for patients with thalassemia syndromes who have had inadequate response with deferoxamine or deferasirox. Furthermore, Italian and U.S. guidelines recommend that clinicians consider deferiprone in combination with deferoxamine as an option in patients with cardiac symptoms or cardiomyopathy.

The adverse reactions of greatest concern for deferiprone are agranulocytosis and neutropenia that may result in severe infection or death. Adverse outcomes due to these conditions can be mitigated by regular monitoring. Furthermore, deferiprone's place in iron chelation therapy is as a final recourse, so the alternative to deferiprone would be entry into a clinical trial for an experimental iron chelator, if available, or almost certain disability or death from iron overload.

There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related sequelae, functioning, or increased survival. FDA approval is based on a reduction in serum ferritin level (primary end point), reduction in liver iron concentration (LIC), and increase in MRI T2* (secondary end points) as determined by reviewing pre-existing clinical data. Only LIC by liver biopsy is considered standard reliable surrogate for measuring iron burden and is considered to be related to clinical benefit. The analysis of pre-existing clinical data showed 52%, 42%, and 62% of patients responded to deferiprone therapy defined as a ≥20% reduction in serum ferritin, ≥20% reduction in LIC, or ≥20% increase in MRI T2*, respectively. However, whether these results translate into clinical benefit remains unclear.

Recommendation:

- Recommend adding deferoxamine as a preferred agent on the PDL.
- Recommend making the oral agents deferasirox and deferiprone non-preferred and using the default non-preferred PA criteria to utilize them as second line agents.

BACKGROUND/CURRENT LANDSCAPE

Deferiprone is one of three FDA-approved drugs to treat iron overload. Deferoxamine (Desferal) was approved in 1968 and deferasirox (Exjade) in 2005 for the treatment of chronic iron overload due to transfusion-dependent anemias or blood transfusions, respectively.[3,4] While the U.S. approved deferiprone in 2011, the European Union approved the drug in 1999. Most of the more than 60 countries that have approved deferiprone have limited its use to treating iron overload in patients with thalassemia major for whom deferoxamine therapy has been contraindicated or inadequate. The FDA also has limited deferiprone so that it will serve as second-line therapy in patients with transfusion-dependent thalassemia syndromes.[5]

Thalassemia is a hereditary disorder characterized by decreased hemoglobin production and red blood cell survival. Patients with severe manifestations of thalassemia require red blood cell transfusions and iron chelation therapy or allogeneic bone marrow transplant.[6,7]

Patients with transfusion-dependent thalassemia develop iron overload because the body is unable to excrete excess iron. This problem is more pronounced in patients with thalassemia because their gastrointestinal tracts absorb more iron than normal. The excess non-transferrin-bound iron deposits in tissues as free iron, damaging and disrupting the normal function of organs such as the liver, pancreas, heart, and endocrine glands. Iron toxicity can cause diabetes, hypogonadism, hypothyroidism, adrenal insufficiency, hepatic fibrosis, cardiac arrhythmias and failure, and more.[7]

Iron overload in thalassemia is treated using chelators that bind iron in the blood and organs. Deferoxamine often is used as first-line therapy for iron overload in thalassemia; however, not all patients can tolerate deferoxamine because of its side effects. About 32% of thalassemia patients report complications with deferoxamine requiring modifications of dose or route of administration.[11] The rate of compliance with deferoxamine has been estimated to be 70% due to complex dosing and administration.[12] As a once daily orally administered iron chelator, deferasirox overcomes the administration-related noncompliance associated with deferoxamine. Its accelerated approval was based on LIC, considered a measure of clinical benefit, and serum ferritin levels, a surrogate endpoint; however, increased survival has yet to be demonstrated or clinical benefit confirmed.[4,13] As with deferoxamine, patients may experience deferasirox-associated side effects resulting in dose reduction or discontinuation, and some patients may have inadequate iron elimination for unexplained physiologic reasons.

Laboratory tests for assessing iron levels include serum ferritin, imaging, and LIC by liver biopsy.[7] Liver biopsy is the generally accepted standard for assessing LIC, because 90% of excess iron is deposited in the liver.[13] The suggested optimal range for LIC for chelation therapy in transfusional overload is 3.2 to 7 mg Fe/g dry weight. An LIC value of 7 mg Fe/g dry weight is considered the threshold for increased risk of sequelae due to iron overload.[14] Because liver iron does not linearly correlate with cardiac iron, alternative methods of accessing iron have been employed for the heart.[15] MRI T2* detects cardiac iron deposition, which is indicated by a decrease in T2* relaxation values measured in milliseconds (msec). In adults with thalassemia major, left ventricular dysfunction increases as the T2* falls below 20 msec.[7,14] The most commonly used test of iron burden is serum ferritin level. However, ferritin is an acute-phase reactant whose level is influenced by a variety of factors that limit its accuracy, such as the presence of inflammation, infection, and vitamin C deficiency.[7,16] Also, the relationship between serum ferritin level and treatment for iron excess is non-linear.[7] Nevertheless, serum ferritin levels <2500 µg/L with deferoxamine is associated with lower risk of cardiac dysfunction and death.[14]

The Standards of Care Guidelines for Thalassemia published by the Children's Hospital and Research Center Oakland (CHRCO), one of seven thalassemia treatment centers funded by the CDC, has not been updated since deferiprone's approval.[15] However, the guidelines do address deferiprone's use as an investigational drug and states the following with regard to the presence of cardiac symptom and cardiomyopathy, respectively:

- Presence of cardiac symptoms (arrhythmia or decreased left ventricular ejection fraction): *the patient must be exposed to chelator 24 hours per day, 7 days per week. This treatment is considered to be emergent. Multiple drug therapy—in particular, therapy involving deferiprone—should be considered in this circumstance. . . Patients whose cardiac T2* is less than 10 ms and who do not have cardiomyopathy should receive maximum therapy (see Table 5.1). Consultation with an iron chelation specialist is strongly recommended in the management of all patients with an abnormal cardiac T2*.*

- From Table 5.1, presence of iron-induced cardiomyopathy T2* <20 ms; or T2* <10 ms without cardiomyopathy: *Maximum chelation: 24-hour deferoxamine therapy; consider deferiprone . . . . Monitor intensively with cardiology consulation and iron chelation specialist.*

Recommendations for deferiprone's use as an approved drug in the EU are presented in Italian guidelines:

From the Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders:[1] *For patients with evidence of non-compliance to deferoxamine, or with severe adverse effects from deferoxamine which preclude its use, but without existing or pending severe iron overload, an oral iron chelator should be used as an alternative to deferoxamine therapy (level D). The lack of studies comparing deferiprone with deferasirox in thalassemia major or related disorders did not allow the panel to recommend one of them on the basis of scientific evidence on long-term efficacy. The panel felt justified in recommending deferasirox as the alternative therapy to deferoxamine on the basis of its better safety profile compared with deferiprone (level D). Deferiprone should be considered in the case of resistance or intolerance to deferasirox (level D).Patients who develop severe iron overload (serum ferritin higher than 3,000 ng/mL maintained for three months at least, liver iron content higher than 15 mg/g d.w., or heart T2* <12 msec) or overt iron-related cardiomyopathy (left ventricular ejection fraction <55%, arrhythmias, cardiac failure) should receive "intensive" or "combined" iron chelation therapy. The panel judged that the first choice for combined therapy is deferoxamine associated with deferiprone (level B). Patients who develop life-threatening cardiomyopathy should receive continuous intensive or combined chelation therapy.*

From the Society for the Study of Thalassemia and Hemoglobinopathies Guideline recommendations for heart complications in thalassemia major:[2]

- For prevention of iron-induced cardiac dysfunction: *The ability of iron chelating efficacy of desferrioxamine and deferiprone (L1) at the standard dosage (50 mg/kg over 8–10 h/5 days per week and 75 mg/kg/7 days per week, respectively) appears to be superimposable after 1 year of treatment in terms of ferritin reduction (I,A . . . . In summary (IIa,B):. . . . (2) The choice of the drug to be used must be individualized; intolerance, low compliance, onset of side effects, and not least, personal evaluations of the physician or of the patient, can lead to the choice of one of the most important drugs; (3)The combined or associated use of deferiprone plus desferrioxamine improves chelation, but also the risk of more marked side effects; (4) The dosages of the drugs or of their combination must be suited to obtain therapeutic targets that are seen as valid.*

- For chelation treatment in iron-induced myocardial dysfunction: *When clinically suggested, the modalities of administration are (1) continuous subcutaneous administration of desferroxamine (40–60 mg/kg every day) (I,B); (2) In selected cases, continuous administration of desferrioxamine through the peripheral venous pathway or through a central catheter . . . . . .(I,C); (3) Combined or associated desferrioxamine (40–50 mg/kg) and deferiprone (70–80 mg/kg) treatment has been reported in clinical practice (IIb,C).*

Efficacy:

Although deferiprone has been approved in the EU since 1999, studies with deferiprone have been inconsistent and adequate, prospective, randomized, well-controlled clinical trials to assess the clinical benefit of deferiprone are still lacking.[1,2,12] The FDA based accelerated approval for deferiprone on reduction in serum ferritin levels (primary outcome) and LIC and MRI T2* (secondary outcomes) as demonstrated by an open-label, uncontrolled, retrospective analysis of pre-existing clinical data entitled "Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate" (LA36-0310). This study was completed after the original New Drug Application submission failed to achieve FDA approval. The

initial NDA was based on a controlled trial of 61 adult patients with thalassemia randomized to deferiprone or deferoxamine therapy, with change in cardiac iron burden assessed by MRI T2* as the primary efficacy end point and serum ferritin an LIC as secondary end points. The FDA cited several deficiencies in the NDA, including insufficient evidence of efficacy, insufficient information to establish the clinical benefit of incremental changes in cardiac MRI T2* (e.g., improved survival, symptoms, functional status), lack of survival data, absence of pediatric patients, and more. Finally, the FDA stated "published literature does not consistently support the efficacy or safety of deferiprone. Some studies have suggested loss of effectiveness over expanded time periods and others have suggested increased liver toxicity among patients who remain on prolonged deferiprone therapy. . . . We note that other reports have not cited these problems."[13]

The analysis of multiple studies provided the FDA with evidence for deferiprone to achieve approval as a second-line iron chelator for patients with transfusional iron overload who have had inadequate response to previous chelation therapy. Study LA36-0310 pooled a subset of inadequately responsive patients (defined as serum ferritin >2500 µg/L, cardiac MRI T2* <20 msec, and LIC >7 mg/g dry weight) from 12 previous clinical studies totaling 264 patients. The primary efficacy end point was change in serum ferritin and the secondary end points were change in LIC and cardiac MRI T2* from baseline to within 1 year of deferiprone therapy (end of study). Treatment success for the primary and secondary end points were defined as ≥20% decline in serum ferritin, ≥20% increase in cardiac MRI T2*, and ≥20% decline in LIC. Serum ferritin was chosen as the primary end point because it was the only measure all of the studies had in common.

The vast majority of patients included in the study had β-thalassemia (94.3%) and had been previously treated with deferoxamine (94.6%). Only 27% of patients had been treated with deferiprone for 1 year or longer and 76% had been treated for at least 6 months. Most patients had received a deferiprone dose of 75 mg/kg/day (76.9%), while 17.8% and 5.3% of patients had received 100 mg/kg/day or 50 mg/kg/day, respectively.

The analysis showed 52% (n=136/264) of patients had a ≥20% decline in serum ferritin from baseline to end of study (up to 1 year of deferiprone therapy). The mean change in serum ferritin was a decrease of 962 µg/L (range 10385 µg/L decrease to 10002 µg/L increase). Fifty percent of patients achieved a ≥20% decline in serum ferritin in each of three subanalyses that excluded patients who had taken both deferiprone and deferoxamine or taken pediatric deferiprone solution or been at one study site that had questionable data quality.

The success rate also was achieved for the secondary analyses, with 42% of patients (n=49/117; CI: 33% to 51%) achieving a ≥20% decline in LIC and 62% (n=24/39; CI: 45% to 77%) a ≥20% increase in cardiac MRI T2*. The mean change in LIC was a decrease of 1.7 mg Fe/g dry weight (range 32.6 mg Fe/g decrease to 14.5 mg Fe/g increase). The mean change in MRI T2* was an increase of 3.3 msec (range 2 msec decrease to 12.7 m sec increase).

This study was rated "poor" and presented numerous limitations to the evaluation of the efficacy of deferiprone as follows:

- Serum ferritin is not an optimal end point, as serum ferritin is an inaccurate as a measure of body iron stores.
- Data are lacking on the clinical benefit of a ≥20% decrease in ferritin.
- The better measure, LIC, showed the weakest results for efficacy, and LIC was available for only 117 patients.
- The change in MRI T2* was small (3.3 msec), and data are lacking on the relationship between incremental changes in MRI T2* and cardiac function.
- Data were limited with regard to duration of response and dose-response relationship.
- Treatment compliance was not assessed.
- The population for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin, as 228 could be evaluated for serum ferritin only, 68 for LIC only, 9 for MRI T2* only, 31 for ferritin and LIC, 12 for ferritin and MRI T2*, 25 for LIC and MRI T2*, and 7 for all three tests.
- The study was non-randomized and single-arm with missing data.
- The studies used in the analysis were heterogeneous, differing in treatment regimens studied, end points and objectives, methods, follow-up periods, patient selection criteria and baseline characteristics, and more.
- Patient information was incomplete with regard to prior therapies.

- The reasons for response or non-response are unclear and may include dose prescribed, adherence to treatment, or blood transfusion rate, in addition to deferiprone pharmacology. According the FDA Statistical Review, "It is unclear whether the efficacy shown in the study is solely due to the Ferriprox therapy, and the interpretation of these analysis results should be taken cautiously."[13]

Several questions remained unaddressed by the study, including:

- What are deferiprone's effects on morbidity and mortality?
- What are the clinical benefits of long-term use?
- How can deferiprone be used in prophylaxis?
- What are the optimum treatment regimens for deferiprone in adults and in pediatric patients?
- How does deferiprone's efficacy in monotherapy or in combination compare to that of deferoxamine or deferasirox?

Safety:

The most serious adverse reaction reported in pooled data collected from 642 patients who participated in single arm or active-controlled clinical studies with deferiprone were agranulocytosis (1.7%; NNH 59) and neutropenia (6.2%; NNH 16), for which deferiprone carries a black box warning noting the potential for death from agranulocytosis or neutropenia. Thirteen deaths due to agranulocytosis-associated sepsis have been reported in the European Union's post-marketing surveillance database. The most common adverse reactions reported during clinical trials were chromaturia (14.6%), nausea (12.6%), vomiting (9.8%), and abdominal pain (10.4%). Gastrointestinal upset caused 1.6% of patients to discontinue therapy in clinical trials. Another noted concern was deferiprone's potential to cause hepatotoxicity. Elevations in ALT or AST were observed in 7.5% (NNH 13) patients and resulted in 0.78% discontinuing therapy.

Unanswered Safety Questions: What are the relationships between exposure to deferiprone (Cmax and AUC) to response and safety? Does deferiprone cause QT prolongation? What are the effects of age, gender, race, and renal and hepatic impairment on exposure to deferiprone and its metabolite? What drugs interact with deferiprone? What is the incidence of agranulocytosis leading to the death because of deferiprone? What is the incidence of hepatotoxicity? Is deferiprone excreted in breast milk and, if so, does it cause harm to infants? What are the adverse effects of long-term use?

COMPARATIVE CLINICAL EFFICACY
Relevant Endpoints:

1) **E*fficacy***: Increased survival, improvement in disease-related sequelae, prevention of iron-induced sequelae
2) **S*afety:*** Agranulocytosis and neutropenia

Study Endpoints:

1) **E*fficacy:*** the change in serum ferritin from baseline to completion of up to one year of therapy, defined as the observation closest to one year in a period of 15 months or at 12 ± 3 months. For subjects that stopped the study early, the value closest to the stopping date was used. Patients who had a decline in serum ferritin of at least 20% over that time period were considered successfully treated, and the trial would be deemed to show evidence of efficacy if at least 20% of patients achieved the described efficacy endpoint
2) **S*afety*:** None

Evidence Table[13]

Ref./Study Design	Drug Regimens	Patient Population[1]	N^, a	Duration	Efficacy Results[2] (CI, p-values)	ARR/ NNT[2,3]	Safety Results (CI, p-values)	ARR/ NNH[2,3]	Quality Rating/Comments[4]
LA36-0310									Poor
open-label, uncontrolled, retrospective analysis of pre-existing clinical data	35 to 100 mg/kg/day administered orally as a tablet or oral solution (The great majority of patients received tablets at a dose of 75 mg/kg/d in 3 divided doses, although some patients received higher or lower doses)	Inclusion criteria: • Treatment with deferiprone • At least a single baseline value for serum ferritin, LIC or MRI T2* available • Follow-up assessment of serum ferritin, LIC or MRI T2* after initiation of deferiprone and within one year of therapy • Had been receiving standard iron chelation therapy with either deferoxamine or deferasirox and before receiving deferiprone had one or more of the following: o Serum ferritin > 2,500 µg/L o Cardiac MRI T2* < 20 ms o LIC > 7 mg/g dry weight Exclusion criteria: • Naïve to iron chelation therapy • Never received deferiprone • No data on serum ferritin, LIC or MRI T2* either while receiving standard chelation therapy or after initiation of deferiprone, or both • Had had an improvement in any of the measures of iron burden of ≥ 20% related to	264 ferritin 117 LIC 39 T2*	up to 12 months	Primary analysis: % patients with ≥20% reduction in serum ferritin: 52% (CI: 45–58%) Secondary analysis: % patients with ≥20% reduction in LIC: 42% (CI: 33–51%) % patients with ≥20% increase in MRI T2*: 62% (CI: 45–77%)	N/A N/A N/A	Not assessed	N/A	Internal Validity RoB: Selection- The study is non-randomized and single-arm with missing data Performance- The studies used in the analysis were heterogeneous, differing in treatment regimens studied, end points and objectives, methods, follow-up periods, patient selection criteria and baseline characteristics, and more. Attrition- Last observation carried forward (LOCF) used for drop-outs. External Validity: Patient Characteristics- Patient information was incomplete with regard to prior therapies. There were only 2 black subjects in serum ferritin group and 0 in LIC and MRI groups. Outcomes- • Serum ferritin is a surrogate end point and lacks specificity as a measure of body iron stores. • The better measure, LIC, showed the weakest results for efficacy, and LIC was available for only 117 patients.

		chelator therapy within the year prior to consideration for enrollment Demographics of ITT population for primary endpoint: White 73% Asian 17% Black 1% Unknown 8% Multiracial 0.4% Male 45% Mean age 20.1 + or - 12.3 Underlying disease: B-thal syndrome: 94.3% Sickle cell: 1.1% Myelofibrosis: 1.9% Deferiprone dose: 75 mg/kg/d: 76.9% 100 mg/kg/d: 17.8% 50 mg/kg/d: 5.3% Prior chelator: Deferoxamine: 94.6% Deferasirox: 3% Deferox+deferasirox: 2.2% Deferiprone treatment duration: ≥ 1 year: 27% ≥6 months< 1 year: 76% Mean serum ferritin: 4416 μg/L							• For serum ferritin endpoint: There was a wide variability of success rate (26-100%) among the various trials. • The change in MRI T2* was small (3.3 msec) and data are lacking on the relationship between incremental changes in MRI T2* and cardiac function. • Data were limited with regard to duration of response and dose-response relationship. • Treatment compliance was not assessed. • The population for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin, as 228 could be evaluated for serum ferritin only, 68 for LIC only, 9 for MRI T2* only, 31 for ferritin and LIC, 12 for ferritin and MRI T2*, 25 for LIC and MRI T2*, and 7 for all three tests. • The reasons for response or non-response are unclear and may include dose prescribed, adherence to treatment, or blood transfusion rate, in addition to deferiprone pharmacology

[1]Tests: MRI T2*: magnetic resonance imaging T2-star, LIC: liver iron concentration
[2]Results abbreviations: ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval.
[3]NNT/NNH are reported only for statistically significant results
[4]Quality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
^Modified ITT: patients that had taken at least one dose of deferiprone and had at least one post-baseline measurement of an efficacy variable
[a]264 (from 12 studies) were eligible for the serum ferritin criterion, 117 (from 10 studies) were eligible for the LIC criterion and 39 (from 5 studies) were eligible for the cardiac MRI T2* criterion

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY
Deferiprone is a chelator with an affinity for ferric ion (iron III), binding with ferric ions to form neutral 3:1 (deferiprone:iron) complexes.

DRUG SAFETY

Data used for deferiprone's safety profile came from the European Union's post-approval adverse event reporting and pooled data from the patients who participated in the individual studies used in study LA36-0310. Both the pooled data and the database reported chromaturia, nausea, vomiting, and arthralgia as the most frequent adverse drug reactions. Agranulocytosis, the clinically most important adverse reaction, was reported in 1.7% (NNH 59) of patients in the database and 1.3% in the study. Thirteen reports of death due to agranulocytosis-associated sepsis and 94 reports of agranulocytosis appear in EU surveillance. Five to 10% of patients participating in the studies used for LA36-0310 developed neutropenia. Of the 642 patients in the clinical trials safety database, three experienced serious hepatobiliary reactions (cholelithiasis, hepatitis, and hepatic congestion), one torsades de pointes, one seizure, and one Henoch-Schönlein purpura. Hepatotoxicity is difficult to assess as liver disease can occur in thalassemia patients without chelation therapy and a large percentage of patients have hepatitis C.[13]

Serious (REMS, Black Box Warnings, Contraindications):[5]

Black box warning:

- Deferiprone can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis.
- Measure the absolute neutrophil count (ANC) before starting deferiprone and monitor the ANC weekly on therapy. Interrupt deferiprone therapy if neutropenia develops.
- Interrupt deferiprone if infection develops and monitor the ANC more frequently.
- Advise patients taking deferiprone to report immediately any symptoms indicative of infection.

Contraindications: Hypersensitivity to the deferiprone product. Periorbital edema with skin rash, Henoch-Schönlein purpura, and urticaria have been reported post-marketing.

Precautions:

Agranulocytosis that may result in death, neutropenia, decreased plasma zinc concentrations, and increased ALT and AST values have been observed with Ferriprox therapy. Although a QT study has not been conducted, one patient with a history of QT prolongation experienced Torsades de Pointes with deferiprone therapy. Therefore, deferiprone should be used cautiously in patients who may have increased risk for QT interval.

Monitoring[5]

Monitor for symptoms of arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizure) and symptoms of infection. Measure the absolute neutrophil count (ANC) before starting deferiprone therapy. Monitor ANC weekly while on therapy and more frequently if infection develops. Monitor serum ALT monthly. Discontinue deferiprone if agranulocytosis (ANC < 0.5 x 10^9/L) or neutropenia (ANC <1.5 x 109/L and > 0.5 x 10^9/L) occur unless the benefits outweigh the risks. Interrupt deferiprone therapy if infection occurs, and consider interruption if a persistent increase in serum transaminase levels develops. Monitor plasma zinc levels and prescribe zinc supplementation if deficiency is evident.

Should neutropenia occur, obtain complete blood cell, absolute neutrophil, and platelet counts daily until recovery.

Tolerability (Drop-out rates, management strategies)[5]

The most frequent adverse reactions reported in clinical trials were gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, which resulted in 1.6% of patients discontinuing therapy. In clinical trials, 1.7% of patients experienced agranulocytosis. There have been reports of agranulocytosis leading to death. In clinical studies, 7.5% of 642 subjects developed increased ALT values, resulting in five (0.78%) subjects discontinuing the drug due to increased serum ALT or AST levels.

Pregnancy/Lactation rating[5]
Category D. Animal studies indicate deferiprone can cause fetal harm, including malformation at doses equivalent to 3% to 4% of the maximum recommended human dose (MRHD) based on body surface area and embryofetal death, as well as maternal toxicity, at doses equivalent 32% of the MRHD. Pregnancy should be avoided when taking deferiprone.

It is unknown whether deferiprone is excreted in human milk.

Carcinogenesis, Mutagenesis, Impairment of Fertility[5]
Although carcinogenicity studies have not been performed, finding tumor formation in carcinogenicity studies is considered likely given genotoxicity results and the findings of mammary gland hyperplasia and mammary gland tumors in rats treated in a 52-week toxicology study. Deferiprone was positive in an in vitro mouse lymphoma cell assay. Deferiprone was clastogenic in chromosomal aberration tests and bone marrow micronucleus assays. Deferiprone was negative in the Ames bacterial reverse mutation test. Deferiprone had no effects on male or female fertility or reproductive function at 25% of the MRHD.

Unanswered safety questions:
What are the relationships between exposure to deferiprone (Cmax and AUC) to response and safety? Does deferiprone cause QT prolongation? What are the effects of age, gender, race, and renal and hepatic impairment on exposure to deferiprone and its metabolite? What drugs interact with deferiprone? What is the incidence of agranulocytosis leading to the death because of deferiprone? What is the incidence of hepatotoxicity? Is deferiprone excreted in breast milk and, if so, does it cause harm to infants? What are the adverse effects of long-term use?

Dose Index (efficacy/toxic)[5]
Children receiving 2.5 to 3 times the recommended dose for more than one year have developed reversible neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements, and axial hypotonia.

No cases of acute overdose have been reported. No specific antidote for deferiprone overdose exists.

Look-alike / Sound-alike (LA/SA) Error Risk Potential
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexicomp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	ISMP	Clinical Judgment
LA/SA for deferiprone	deferoxamine deferasirox	Not available	None	None
LA/SA for Ferriprox	None	Not available	None	None

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	Not given
Cmax	20 mcg/mL*
Protein Binding	<10%
Elimination	75% to 90% in urine primarily as metabolite
Half-Life	1.9 hours
Metabolism	UGT 1A6

*Although administration with food decreased Cmax by 38% and AUC by 10%, dose adjustment is unnecessary.

ALLERGIES/INTERACTIONS[13]

Drug-Drug:

Separate by at least 4 hours the administration of deferiprone and other medications or supplements containing polyvalent cations such as iron, aluminum, and zinc

Avoid concomitant use with drugs associated with neutropenia or agranulocytosis, otherwise closely monitor the absolute neutrophil count.

Closely monitor patients for adverse reactions when deferiprone is used concomitantly with a UGT 1A6 inhibitor, such as silymarin (milk thistle), as the effect of coadministration with UGT 1A6 inhibitors has not been evaluated. Coadministration with such drugs may require lowering the dose of or interrupting deferiprone.

Food-Drug: Not studied

Allergy/Cross Reactive Substances: None

ADVERSE REACTIONS[5]

The following table represents pooled data from 642 patients who participated in single-arm or active-controlled clinical studies.

Table 2: Adverse drug reactions occurring in ≥ 1% of 642 Ferriprox-treated patient

Body System Preferred Term	% Subjects
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine Aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate Aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5
URINARY DISORDERS	
Chromaturia	14.6

DOSE & AVAILABILITY[5]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
25 mg/kg to a maximum of 33 mg/kg	500 mg tablets	oral	Three times daily	Efficacy and safety not evaluated	Efficacy and safety not evaluated	Efficacy and safety not established	Efficacy and safety not established. Start at the low end of the dosing range.	• Round dose to the nearest 250 mg (half-tablet). • Tailor dose to patient's response and therapeutic goals (maintenance or reduction of body iron burden). • Monitor serum ferritin concentration every two to three months. Consider temporarily interrupting deferiprone therapy if serum ferritin consistently falls below 500 mcg/L. • The relationship between deferiprone dose and the amount of iron eliminated from the body has not been assessed. • Dose proportionality over the labeled dosage range has not been studied.

Appendix 2: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.

5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf