CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021825Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 28, 2011
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21-825
Applicant	ApoPharma Inc.
Date of Submission	April 13, 2011
PDUFA Goal Date	October 14, 2011
Proprietary Name / Established (USAN) names	Ferriprox (deferiprone)
Dosage forms / Strength	500 mg film-coated tablets
Proposed Indication(s)	for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate
Recommended:	Approval for revised indication: "for the treatment of patients with transfusional iron overload in patients with thalassemia syndromes when current chelation therapy is inadequate"

Cross Discipline Team Leader Review Template

1. Introduction

Ferriprox (deferiprone) is an orally active iron chelator developed for use in treating iron overload. This is the second review cycle for this product. The NDA was initially submitted 1/29/2009 for the indication, "treatment of iron overload in patients with transfusion-dependent thalassemia and for treatment in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate". A complete response (CR) letter was issued on 11/30/2009. The current resubmission (received 4/14/2011) seeks approval of deferiprone for the indication: "for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate." The proposed dose is deferiprone 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b) (4) mg/kg body weight.

2. Background

Patients with certain inherited anemias (importantly β-thalassemia and increasingly sickle cell disease in the U.S.) require frequent transfusion of red blood cells beginning at a young age to offset anemia that occurs because of inability to manufacture normal hemoglobin. Normal dietary absorption is about 1 mg daily which maintains a total body iron of approximately 3 to 5 grams in adults. One unit of packed red blood cells contains about 200 mg of iron. Because the body has no physiologic mechanism to excrete excess iron, repeated red blood cell

transfusions over time result in massive iron overload. The excess iron becomes deposited in tissues and causes tissue damage due to iron-catalyzed peroxidation of membrane lipids and leads to morbidity and often eventually mortality, mainly due to cardiac damage. The liver and endocrine organs also are notably affected. Assessment of liver iron content (LIC) has been the generally accepted standard for assessment of body iron burden; however, serum ferritin, a nonspecific parameter, is commonly followed clinically.

Currently available treatment options for management of iron overload due to transfusions include Desferal (deferoxamine mesylate), an injectable iron chelator approved in 1968 and Exjade (deferasirox), an orally active iron chelator approved in 2005.

Deferiprone binds iron in a 3:1 complex which is then excreted in the urine. The drug was first administered to humans in 1987, was approved in the European Union in 1999 and currently is approved in 61 countries, mostly for the indication of the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate.

The initial NDA submission provided a single randomized controlled trial (Study LA16-0102) comparing the use of deferiprone versus the use of deferoxamine in removing excess cardiac iron in subjects with thalassemia major. The study used a primary efficacy endpoint that employed magnetic resonance imaging of the heart (cardiac MRI) with measurement of a parameter termed T2* (T2 star) to evaluate extent of iron overload and effectiveness of chelation therapy. The primary efficacy analysis showed a 3.9 msec increase in cardiac MRI T2* from baseline to 12 months in the deferiprone treatment group and 2.3 msec increase in the deferoxamine treatment group but no significant correlation between change in cardiac MRI T2* and measures of cardiac function and there were no differences between treatments in change in liver iron concentration (LIC). A complete response (CR) letter was issued on 11/30/2009 citing a number of clinical deficiencies and well as deficiencies for Clinical Pharmacology, product quality, and facility inspections. See Dr. George Shashaty's Clinical Review (10/19/2009) for details of the first cycle clinical review. See my Cross-Disciplinary Team Leader (CDTL) review (11/25/2009; addendum 12/31/2009) and Dr. Dwaine Rieves' Division Director Summary Review (11/20/2009) for a summary of issues from the first cycle review.

The current resubmission narrows the indication from the initially proposed "treatment of iron overload in patients with transfusion-dependent thalassemia and treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate" to the currently proposed "treatment of patients with transfusional iron overload when current chelation therapy is inadequate." A single retrospective, single-arm study (LA36-0310) is submitted for the indication. Results of the study are discussed under section "7. Clinical/Statistical –Efficacy" below.

3. CMC

The Chemistry, Manufacturing and Controls (CMC) Review (W.M. Adams, Ph.D., final signature 9/27/2009) states, "From a CMC standpoint, this application is recommended for

approval pending the receipt of an overall acceptable recommendation from the Office of Compliance. The submission is complete and all other CMC review issues have been resolved. Insert the following language into the action letter: Based on the stability data provided in your application, the drug product is granted a 24-month expiry when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF)." There are no CMC recommendations for post-marketing commitments.

4. Nonclinical Pharmacology/Toxicology

Phararmacology/Toxicology Review during the first cycle noted that lifetime carcinogenicity studies had not been conducted but the sponsor's proposal to conduct a 2-year carcinogenicity study in rats and a 6-month study in p53 knockout mice during Phase 4 is adequate. Pharmacology found the application acceptable for approval with appropriate warnings in the product labeling regarding the genotoxicity and carcinogenic risk and fetal and developmental toxicity (Pregnancy Category C) (D. E. Bailey, Ph.D. (reviews signed 6/27/07, 8/4/08 and 9/22/09). At the time of this CDTL review Pharmacology/Toxicology review for the current review cycle has not been finalized.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology review was completed by Joseph Grillo, Pharm.D. (final signature, 9/21/2011). The review stated that, "From a clinical pharmacology perspective, this resubmission of the original application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with deferiprone treatment." Recommended postmarketing requirements included that the sponsor: Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment; conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment and; conduct a TQT assessment for deferiprone. In addition, the review recommended that the sponsor conduct *in vitro* studies to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone to determine the need for additional *in vivo* drug interaction trials. Additional comments for the sponsor were included in the review.

In an additional consultation review at the request of the Division of Hematology Products, Clinical Pharmacology reviewed the bioavailability of the deferiprone solution formulation used in ApoPharma's pediatric study LA30-0307 compared to the bioavailability of the to-be-marketed tablets (Joseph Grillo, Pharm.D., final signature 9/21/2011). The review found that the deferiprone solution formulation used in the submitted bioequivalence study (LA21-BE) is bioequivalent to the Ferriprox tablet formulation. The same deferiprone solution formulation was used in trial LA30-0307. Clinical Pharmacology deferred to CMC regarding the integrity of the deferiprone solution batches used in these studies.

The Office of New Drugs Quality Assessment (ONDQA) review conducted by Tien-Mien Chen, Ph.D. (9/16/2011) identified a need for the sponsor to revise the dissolution acceptance criterion to change from "**Q =** (b) (4) and indicated that the sponsor needed to provide an updated specification sheet for the product including the revised criterion for the dissolution test. The deficiency was communicated to the sponsor and the sponsor replied. Review of the sponsor's reply (9/25/2011 review, signed by Angelica Dorantes, Ph.D.) found the sponsor's response acceptable agreeing with the sponsor that the provided dissolution data support an acceptance criterion of Q= (b) (4) in 45 minutes and concluded that, "From the Biopharmaceutics perspective, NDA 21-825 is recommended for approval."

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

In this resubmission a single study (LA36-0310) in which data from patients in the completed studies identified as being inadequately treated with other iron chelators were analyzed examining change in serum ferritin levels from baseline up to one year after starting deferiprone was submitted. The sponsor's primary efficacy analysis showed 136 of 264 patients (52%) had a 20% or greater decrease in serum ferritin from baseline to end of study. See the Clinical Review (Dr. George Shashaty, 9/16/2011), the Statistical Review (Qing Xu, Ph.D., 9/16/2011) and my Medical Team Leader review (signed 9/27/2011) for detailed presentation and discussion of Study LA36-0310. The Clinical and Statistical reviews identified a number of deficiencies of the study design (including that it was retrospective, single arm, pooled patients from heterogeneous studies and had limited information on prior treatment) that limit interpretation of the study results.

The Clinical Review (Dr. George Shashaty, 9/16/2011) recommended that, "if the sponsor agrees to change the indication to "the treatment of patients with thalassemia with transfusional iron overload when previous chelation therapy with other approved iron chelators has been unsuccessful", deferiprone should receive Accelerated Approval under the requirements of 21CFR314.500-314.560 (Subpart H- Accelerated Approval of New Drugs for Serious of Life-Threatening Illnesses). The Secondary Medical Team Review concurs with the recommendation of Accelerated Approval for the indication revised as per Dr. Shashaty (Kathy Robie Suh, M.D., Ph.D., signed 9/27/2011)

8. Safety

Updated safety information was reviewed by Dr. George Shashaty in his Clinical Review (9/16/2011). The safety profile of deferiprone for the resubmission is not changed from the profile described during the first cycle review. The major safety consideration is agranulocytosis which occurred in 1.7% of patients in the clinical studies. In the post-

European Union marketing surveillance there have been 94 reports of agranulocytosis including 13 deaths.

Deferiprone is genotoxic and teratogenic as described in the first cycle Pharmacology/Toxicology review (David Bailey, Ph.D., reviews signed 6/27/2007, 8/4/2008 and 9/22/2009) and this risk should be reflected in the labeling.

9. Advisory Committee Meeting

A meeting of the Oncology Drugs Advisory Committee (ODAC) was held on September 14, 2011 to discuss the deferiprone application. As Dr. Shashaty states in his review, "The agenda included presentations made by the sponsor and FDA, and an open public hearing. Members of the committee addressed questions to the sponsor and FDA. There was a discussion of the merits of the application. In response to the question "Is there a favorable benefit/risk profile for deferiprone in the treatment of patients in whom current chelation therapy is inadequate?", the Committee, by a margin of 10 to 2, voted in the affirmative."

10. Pediatrics

The current application does not seek approval for use of deferiprone in pediatric patients. Also, the drug is an orphan product for the indication. Nevertheless, the indication is relevant to pediatric populations and the sponsor has conducted a study of a deferiprone oral solution in pediatric patients. Clinical Pharmacology review has determined that the oral formulation used in that study is bioequivalent to the tablet formulation. (See discussion under "5. Clinical Pharmacology/Biopharmaceutics" above).

Maternal and Pediatric Health Team (PMHT) comments have not been finalized at the time of this review. However, the PMHT has participated in labeling discussions.

11. Other Relevant Regulatory Issues

None.

12. Labeling

All the review disciplines have provided relevant recommendations in their reviews and have participated in labeling meetings discussing the wording in the label.

Additional recommendations have been provided by the Division of Drug Marketing, Advertising, and Communications (James S. Dvorsky, 8/30/2011) and these have been considered in the labeling discussions.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The application should be granted Accelerated Approval under Subpart H regulations for the indication: "for treatment of transfusional hemosiderosis in patients with thalassemia who are inadequately treated with other iron chelators."

At the time of this review the recommendation for approval is contingent upon the receipt of an overall acceptable recommendation from the Office of Compliance as per CMC review.

- Risk Benefit Assessment

There continues to be a need for iron chelating agents for use in patients who are not adequately treated with currently available products. While the studies of deferiprone are imperfect in design and provide limited information on clinical effects of deferiprone therapy, the available data for patients with thalassemia who are identified as being inadequately treated with currently available chelators appear to show an adequate benefit risk profile to support approval of deferiprone for use in these patients. As Dr. Shashaty summarizes in his Clinical Review (9/16/2011):

> "Patients with transfusional hemosiderosis treated with either deferoxamine or deferasirox may have an inadequate reduction in total body iron burden. Reasons for this include the difficulty of administration leading to suboptimal compliance, intolerance to drug induced symptoms (particularly gastrointestinal and dermatological), the development of adverse reactions that lead to dose modifications or withdrawal, or unexplained causes that limit the iron excretion effects of the currently approved iron chelators. For such patients, there are no alternative therapies and, since many of them have a continuing requirement for transfusion therapy, iron overloading progresses, eventually leading to organ dysfunction and, possibly, death. The organ most commonly compromised, and which is the most common cause of death (at least in persons with thalassemia), is the heart. Cardiac failure and arrhythmias are responsible for approximately 70% of deaths in patients with thalassemia (Borgna-Pignatti C et al 2004. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 89:1187-93).
> Therefore, an additional iron chelator would be of utility for such patients, even if there are risks associated with its administration. For deferiprone, whose most important adverse reaction is the development of agranulocytosis (approximately 1.7% of users), because of the lack of alternative drugs, the risks of deferiprone might be acceptable to gain its benefits in persons with thalassemia.
>
> I believe that the indication for the use of deferiprone should be restricted to patients with thalassemia. Approximately 95% of all of the patients in whom the drug was studied had thalassemia as the anemia that led to the requirement for chronic transfusion therapy. There have only been a total of 35 patients with sickle cell disease, myelodysplastic syndrome (MDS) with variants, and other transfusion dependent anemias who have been treated with deferiprone in the clinical studies. All of the non-thalassemic patients were enrolled in a Compassionate Use Treatment protocol (LA-04) and the interpretation of the data from that study is complicated by

the multiplicity of physicians involved, variability in inclusion/exclusion criteria, the adequacy of data regarding efficacy, compliance and safety assessments and the use of concomitant chelators in a number of the enrollees."

I concur with Dr. Shashaty's assessment.

- Recommendation for other Postmarketing Requirements and Commitments

The following are recommendations for postmarketing requirements and commitments that should be considered:

- A registry of patients with thalassemia and transfusion related hemosiderosis who cannot be effectively treated with either deferoxamine or deferasirox with data accumulated for a time span sufficient in length to determine the natural history and the efficacy and safety of the use of deferiprone in these individuals. The registry should focus on mortality and morbidity in patients receiving deferiprone, hepatic function, the development of malignancies and persistence of drug effect on body iron load.
- A prospective randomized safety and efficacy trial in patients with sickle cell disease and transfusion related hemosiderosis who cannot be effectively treated with deferoxamine should be conducted to better address the U.S. population likely to receive deferiprone.
- A prospective randomized trial in patients with thalassemia and transfusion related hemosiderosis who cannot be effectively treated with deferoxamine comparing the efficacy and safety of the use of deferasirox with the efficacy and safety of the use of deferiprone in that population. An alternative acceptable trial in a similar population could compare the use of deferasirox alone with the combination of deferasirox and deferiprone.
- A pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment;
- A pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment and;
- A thorough QT assessment for deferiprone;
- *in vitro* studies to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone to determine the need for additional *in vivo* drug interaction trials.

Evaluation of deferiprone for use in pediatric patients with β-thalassemia should be encouraged.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
09/29/2011