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APPLICATION NUMBER:

021825Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-825 **COMPLETE RESPONSE**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for Ferriprox® (deferiprone) 500 mg Tablet.

We acknowledge receipt of your submissions dated December 21, 2006; March 12 and 28, September 26, and December 21, 2007; March 19 and 27, June 12 and 27, September 15 and 29, October 29, and November 25, 2008; and amendments dated February 17 and 24 (2), March 5, 10 and 17 (2), May 7 and 28, June 9, 15 and 30, July 9 and 16, August 12 and 25, September 3, 9, 15, 22 and 23, October 8, 20 and 27, 2009.

We also acknowledge receipt of your amendments dated August 6 and October 13, 2009, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. The application contains insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling and lacks substantial evidence of efficacy from adequate and well-controlled investigations. Listed below are our requests for additional data, followed by a summary of the basis for these requests.

2. A decrease in the cardiac content of iron, as measured by magnetic resonance imaging (MRI) T2* alterations, was the proposed treatment effect in the single confirmatory study intended to verify deferiprone safety and efficacy. Listed below are requests for additional information if you use this endpoint in any future regulatory submissions:

a. Supply data from at least one additional prospective, randomized, controlled clinical study that verifies the proposed deferiprone treatment effect.

b. Supply data that verify the clinical meaningfulness (e.g., improved survival, symptoms, functional status or other clinical benefits) of incremental changes in cardiac MRI T2* values. These data should establish the minimum millisecond increase in T2* that is indicative of a clinical benefit.

c. In developing subsequent clinical studies, we encourage you to enroll pediatric patients with transfusional hemosiderosis. Data within the submitted confirmatory study were obtained entirely from adult patients.

3. Submit data that verify the absence of a mortality disadvantage when deferiprone is administered over a prolonged time period. These data could be obtained from follow-up survival information for all patients enrolled in Study LA-01 ("Randomized Trial of Deferiprone and Deferoxamine in Thalassemia Major") and Study LA-16-0102 ("Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients"). Alternatively, supply data from other randomized, controlled studies that allow an assessment of survival in comparison to a clinically appropriate control therapy. The need for survival data cannot be addressed by the submission of uncontrolled study data or data from historically controlled/observational-type studies.

4. Submit data that more thoroughly assess the arrhythmogenic potential of deferiprone. In addition to any other information, supply data from an assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers.

5. FDA inspectional findings could not fully verify the accuracy of data submitted by you for Study LA-01, with respect to the Toronto, Canada clinical site. The principal investigator at that site was Dr. Nancy Olivieri. We understand that you terminated that study site in May 1996, prior to study completion. Our comments below pertain solely to data that was generated at that study site prior to the termination of the site. Supply information that addresses the items listed below:

   a. A Good Clinical Practice (GCP) inspection of Dr. Olivieri's data revealed discrepancies between superconducting quantum interference device (SQUID) values verified by source documents at the site in comparison to the data submitted to the NDA.

      Address these discrepancies.

   b. The GCP Inspection of Dr. Olivieri's data also revealed that the liver biopsy iron concentration values reported in the NDA listings as provided by you in 2.2.1 could not be verified by source documents, because the source documents were not available.

Provide all source documents to support the iron content as measured by liver biopsy.

6. With regard to Study LA-01, there appear to be inconsistencies in your analyses of the data and the exclusion of certain subjects and data points from the analysis. Specifically:

   a. Per Data Listing 2.2.2 in the NDA, several iron concentration data points were excluded from analysis and the rationale for each exclusion was provided in this data listing. However, the rationale for exclusion was inconsistently applied in your analyses. For example, Subjects 42, 43, 51, and 55, had all of their iron concentration data excluded from analyses because "patient[s] did not complete 24 months of chelator therapy." However, Subjects 25, 34, 37, and 59, were included in your analyses (as provided in Data Listing 2.2.1) even though these subjects apparently did not receive 24 months of chelator therapy.

      Address this inconsistency.

   b. We also note that Table 12.2, Patient Listing of Discontinued Patients, includes information for subjects from Dr. Olivieri's site from 1997, which was after the study site was terminated. Therefore, you appear to have access to at least some data collected after termination of the site.

      Confirm that all relevant data in your possession at the time of NDA submission, regardless of whether those data were generated after termination of the study site, were included in the application.

We cite the following information as the basis for the clinical requests listed above:

7. You provided data from a single, controlled trial as confirmatory evidence of deferiprone efficacy and safety (Study LA-16-0102). In this study, 61 adult patients were randomized to therapy with either deferiprone or deferoxamine.

   a. Regarding efficacy, you claimed that greater increases in cardiac magnetic resonance measures of T2* were observed in the deferiprone group than in the control group, a primary endpoint outcome which you proposed as indicative of a decrease in cardiac iron and a clinical benefit. However, the supplied data did not establish the specific clinical benefit attributed to the increase in T2* measurements. Additionally, we do not regard the primary endpoint result as a robust observation due to the study's relatively small sample size, which precluded subset and other exploratory analyses.

      Secondary endpoints also were not consistently corroborative of the primary endpoint result. For example, changes in serum ferritin and liver iron concentration were not significantly different between the two study groups.

   b. Regarding safety, adverse events related to elevation of serum alanine aminotransferase levels were reported in 38% of the deferiprone group but in only

13% of the deferoxamine group. In the context of additional concerns (below), this observation signals the potential for deferiprone-induced liver toxicity.

8. The supplied supportive study (LA 12-9907) used an uncontrolled design and statistical features consistent with an exploratory study. Hence, this study was incapable of verifying deferiprone efficacy and safety.

9. The other supplied clinical data are of very limited value to verification of deferiprone effects, particularly when the proposed confirmatory study failed to verify safety and efficacy. The supportive data included the occurrence of an important cardiac arrhythmia (torsade de pointes) that was assessed by a cardiologist as possibly related to deferiprone therapy. Overall, the supportive studies contained numerous deficiencies, such as the use of retrospective designs, relatively small sample sizes, the lack of control groups, missing data and inconsistency in results. Post-marketing reports indicated the occurrence of agranulocytosis followed by death in 13 patients.

10. In consideration of the submitted data, complete and accurate submission of clinical data from Study LA-01 is relevant to the evaluation of deferiprone safety and efficacy because the sample size exceeded that of all other controlled studies. Study LA-01 is also of interest because it used a primary endpoint that has previously been accepted by FDA.

11. 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 (Blood 1998;91:295-300 and the New England Journal of Medicine 1998;339:417-423). We note that other reports have not cited these problems. In the context of the safety and efficacy deficiencies cited above, the inconsistency within the published literature underscores the importance of complete data submission from adequate and well controlled clinical studies that rigorously assess clinically meaningful outcomes, including overall survival.

CLINICAL PHARMACOLOGY

1. Conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with hepatic impairment. Submit the protocol to the Agency prior to conduct of the study for agreement with the study design. Conduct this pharmacokinetic study in a patient population with mild to severe hepatic insufficiency, according to the Child-Pugh classification.

2. Conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with renal impairment. Submit the protocol to the Agency prior to conduct of the study for agreement with the study design. Conduct this pharmacokinetic study in a patient population with mild to severe renal insufficiency.

3. Conduct two *in vitro* studies; one to determine the affect of moderate to strong UDP

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