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APPLICATION NUMBER:

021825Orig1s000

OTHER ACTION LETTERS



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

glucuronosyltransferase (UGT) inhibition and one to determine affect of moderate to strong UGT induction on the metabolism of deferiprone. The results of these studies will determine the need for additional *in vivo* drug interaction studies.

PRODUCT QUALITY

1. "Apotex, Inc." is listed as the site for several method validation studies. Identify the location of this facility and briefly describe the manufacturing and control functions performed at this site. Also, indicate which of these functions are performed in support of the new drug application supported by Drug Master File 10,867.
2. For the drug substance lots used in the method transfer, validation and comparison studies, identify the manufacturing site, date of manufacture and batch size, and provide a certificate of analysis.
3. The submitted analytical method transfer documents (certificates of technology transfer) are not adequate in that the documents are incomplete, the studies they summarize are not sufficient for the intended purpose, and not all sites using these methods have been addressed.
 - a. In each document, clearly identify the location of the initiating and the receiving laboratories and summarize the study protocol.
 - b. For the Residual Solvents method, in each document address specificity, accuracy, precision, linearity and quantitation limit. Spiked samples may be used. Include copies of chromatograms labeled with the peak identity and the system suitability criteria from the specificity study. Address each system suitability criterion.
 - c. For the Assay method, the documents do not address transfer from Apotex Pharmachem to (b) (4) or to Apotex - Etobicoke. In each document, address specificity, accuracy, precision and linearity. Include copies of chromatograms labeled with the peak identity and the SS criteria from the specificity study. Address each system suitability criterion.
 - d. For the Related Substances method, the documents do not address transfer from Apotex Pharmachem to (b) (4) or to Apotex - Etobicoke. In each document, address specificity, accuracy, precision, linearity and quantitation limit. Include copies of chromatograms labeled with the peak identity and the system suitability criteria from the specificity study. Address each system suitability criterion.
4. Regarding the validation summary and comparison study for method AP66-DS-10-SG.01:
 - a. The method description indicates drug substance retention time of (b) (4) as a system suitability criterion. The specificity study reports values (b) (4) and

- the robustness study reports values of (b) (4) for nominal conditions with significant effect for all four method parameters tested. Revise the system suitability criteria for the method such that consistent values for drug substance retention time are obtained with each analysis.
- b. For the specificity study, identify the compounds represented by the peaks with retention times at (b) (4).
 - c. For the method precision study, identify the location of each of the chemists.
 - d. Revise the method comparison study to include data on same set of multiple drug substance lots.
5. Regarding the validation summary and comparison study for method AP66-DS-20-SG.01:
- a. For the specificity study, identify the compounds represented by the peaks with retention times at (b) (4).
 - b. For the method precision study, identify the location of each of the chemists.
 - c. For the robustness study, provide data to address the effect of variations in the cited method parameters on each of the proposed system suitability criteria for drug substance and for (b) (4). Also, provide copies of the chromatograms labeled with each of the system suitability criteria from this study.
 - d. Revise the method comparison study to provide test results for both drug substance and (b) (4) on the same set of multiple drug substance lots which contain impurities. Either spiked or degraded samples may be used.
6. The proposed retest period is based on bulk drug substance stored at ICH long term conditions and the post approval protocol indicates the use of ICH long term conditions. Revise the label storage statement to reflect the current USP controlled room temperature definition (20-25°C with excursions to 40°C). In addition, DMF 10,867 includes stress degradation studies which support a light protection statement. Revise the label storage statement to reflect protection from light.
7. We have reviewed the referenced dissolution profile data and recommend that the dissolution specification be revised to the following:
- Apparatus: USP apparatus II (paddle) at 50 rpm
Medium: 900 mL 0.1N HCl at 37°C
Sampling: Single point with Q = (b) (4).

8. For the drug product lots used in the method transfer, validation and comparison studies, identify the manufacturing site, date of manufacture, batch size, drug substance lot, and provide a certificate of analysis.
9. Regarding method APP66-IMTB-10-SG:
 - a. The methods for drug substance and drug product assay use the same analytical system and differ only in the sample preparation; however the system suitability criterion for drug substance retention time is (b) (4) for drug substance and (b) (4) for drug product. Explain the differences in this criterion.
 - b. The release specification indicates drug identity is established by comparison of retention time and the method description indicates drug identification is by comparison of UV scans. Specify which procedure is to be used and make the correction to the necessary documents.
10. Regarding the validation summary and comparison study for method AP66-IMTB-10-SG:
 - a. The data submitted for the linearity and robustness was that taken from the method validation study for drug substance. Revise these studies to address the effects of drug product and excipients on the test values.
 - b. For the method precision study, identify the location of the chemists referenced in the study.
 - c. For the robustness study, the drug substance retention time is shown to vary significantly with each of the four method parameters evaluated and the retention time for nominal conditions is (b) (4) while the system suitability criterion is (b) (4). Explain the discrepancy and revise the system suitability criteria to obtain a consistent value for drug substance retention time in each analysis.
 - d. Revise the method comparison study to include data on the same set of multiple drug product lots.
11. Regarding the validation summary and comparison study for method AP66-IMTB-20-SG.02:
 - a. The submitted validation summary is the method validation study for drug substance with a cover page indicating the use of drug product. Provide an acceptable method validation study for this method.
 - b. Revise the method comparison study to include data on the same set of multiple drug product lots. Spiked or degrades samples may be used.

12. Regarding the validation summary and comparison study for method AP66-IMTB-41-SG.02:
 - a. Revise the linearity study to use drug product samples instead of drug substance.
 - b. Revise the method comparison study to include drug release profile data (sampling at 10, 20, 30, 45 minutes) on the same set of multiple drug product lots.

13. Regarding the submitted drug product stability data:
 - a. There are completed 60 month studies at ICH long term conditions for four tablet lots manufactured with Apotex Pharmachem material; one tablet lot made with (b) (4) material; and no tablet lots made with (b) (4) material. Provide additional data supporting a 60 month initial expiration date for tablets made with (b) (4) material. Also, specify how the drug product lot numbering system will differentiate between tablets made with drug substance from each of the three possible sites.
 - b. Provide dissolution profiles (10, 20, 30 and 45 minutes) for tablets used in the stability studies.

14. Regarding the proposed Patient Information Leaflet:
 - a. In section 16, revise the storage statement used to reflect the standard USP controlled room temperature statement.
 - b. In section 16, delete the statement (b) (4)
 - c. Identify the location of the lot number and expiration date on the label.

15. DMF 10,867 has been reviewed and found deficient to support approval of this NDA. A deficiency letter detailing the deficiencies has been issued the agent for the DMF holder. These deficiencies must be resolved before the application can be approved.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

FACILITY INSPECTIONS

After a December, 2008 inspection of the Apotex, Inc. (Etobicoke site, Ontario, Canada) manufacturing facility for this application, the Office of Compliance issued a warning letter

dated June 25, 2009, which conveyed cGMP deficiencies at this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21825	----- ORIG-1	----- AOPHARMA INC	----- FERRIPROX (DEFERIPRONE)

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/s/

RICHARD PAZDUR
11/30/2009