DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825

ACCELERATED APPROVAL

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 (FDCA) for Ferriprox® (deferiprone) 500 mg Tablet.

We acknowledge receipt of your amendments dated February 25; April 14, 29; May 6 and 10; June 7, 14, and 22; July 11, 25, and 27; August 12, 19, 22, and 26; September 6, 16, 22, 26, and 29; October 3, 5, 7, 13, and 14, 2011.

The April 14, 2011 submission constituted a complete response to our November 30, 2009 action letter.

This new drug application provides for the use of Ferriprox® (deferiprone) Tablet for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABELS

Submit the final printed container label that is identical to the immediate container label submitted on October 13, 2011 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021825**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. We remind you of your postmarketing requirement specified in your submission dated October 13, 2011.

You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by deferiprone, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530(b), withdraw or modify approval.

Granting of these approvals are contingent upon completion of clinical trials to verify the clinical benefit of deferiprone. These postmarketing trials are subject to the reporting requirements of 21 CFR 314.81.

This requirement, along with required completion dates, is listed below.

PMR 1828-1 Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing. The trial will enroll a sufficient number of patients with sickle cell disease as described above, to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial may enroll patients with other conditions who have developed transfusional iron overload. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration.

Final Protocol Submission:	February 2012
Trial Completion:	January 2016
Final Report Submission:	July 2016

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks for agranulocytosis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1828-2 Establish a registry in order to perform an enhanced pharmacovigilance study of agranulocytosis. Submit a protocol to establish the registry and describe procedures for this enhanced pharmacovigilance prior to commencing the study. Procedures should include: Creation of marketing materials to inform and encourage clinicians to report agranulocytosis events to the sponsor; monitoring of all reported cases and active follow-up to characterize the demographics, recent prior blood counts, concomitant medications, co-existing conditions, duration of drug exposure prior to onset, outcomes of the event, and other factors that may help to characterize the agranulocytosis event. Sponsor also will institute procedures to obtain blood samples from patients with reported cases of agranulocytosis to store for later analysis of possible genetic underlying factors that may predict the risk of agranulocytosis. Submit interim reports annually describing the above results.

Final Protocol Submission:	April 2012
Annual Interim Report #1:	April 2013
Annual Interim Report #2:	April 2014
Annual Interim Report #3:	April 2015
Annual Interim Report #4:	April 2016
Annual Interim Report #5:	April 2017
Annual Interim Report #6:	April 2018
Trial Completion:	October 2018
Final Report Submission:	April 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of QT prolongation, alterations in metabolism and drug effect related to hepatic or renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1828-3 Conduct a clinical trial per ICH E14 to assess the potential for deferiprone to prolong the QT interval. Submit the protocol for IRT review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	December 2013

PMR 1828-4 Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. This pharmacokinetic trial should be conducted in a population with mild to severe hepatic insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that are representative of the indicated population (e.g., age, weight, gender, race). Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	September 2012
Trial Completion:	February 2014
Final Report Submission:	July 2014

PMR 1828-5 Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment. This pharmacokinetic trial should be conducted in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that represent the indicated population (e.g., age, weight, gender, race) to the extent possible. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	September 2012
Trial Completion:	February 2014
Final Report Submission:	July 2014

Submit the protocols to your IND 045724, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 1828-6 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. The results of the *in vitro* evaluations will determine the need for additional *in vivo* drug interaction trials.

The timetable you submitted on October 13, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2012
Study Completion:	July 2013
Final Report Submission:	October 2013

PMC 1828-7 To submit results of the "Tanner" trial comparing the effects of deferoxamine alone to the combination of deferoxamine plus Deferiprone in patients with thalassemia major, reported in the journal "Circulation" in 2007.
Submit the clinical trial report and complete, raw datasets and analysis programs.

The timetable you submitted on October 13, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2012
Trial Completion:	July 2012
Final Report Submission:	October 2012

Submit clinical protocols to your IND 045724 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to the Division of Hematology Products and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
Content of Labeling
Medication Guide
Container Labeling

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

/s/

RICHARD PAZDUR
10/14/2011