CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208030Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA # **Supplement #**	208030
Applicant Name	ApoPharma, Inc.
Date of Submission	November 17, 2014
PDUFA Goal Date	September 17, 2015
Proprietary Name / **Established (USAN) Name**	Ferriprox Deferiprone
Dosage Forms / Strength	Oral Solution 50 g/500 mL (100 mg/mL)
Proposed Indications	For treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Action:	*Approval with No Change in Indication*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Andrew Dmytriuk, M.D./Kathy Robie-Suh, Ph.D., M.D.
Statistical Review	
Pharmacology Toxicology Review	Brenda J. Gehrke, Ph.D., Christopher M. Sheth, Ph.D.
CMC Review	Katherine Windsor, Ph.D./Donghao Lu, Ph.D./Lin Qi, Ph.D./Denise Miller, Ph.D./Zhong Li, Ph.D.
Clinical Pharmacology Review	Sriram Subramaniam, Ph.D./Bahru Habtemariam, Pharm.D.
OMP/DMPP	Morgan Walker, Pharm.D., M.B.A./LaShawn Griffiths, MSHS-PH, BSN/Sharon Mills, B.S.N
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D.
OPDP	James Dvorsky, Pharm.D.
Division of New Drug Bioequivalence Evaluation/OSIS	John Kadavil, Ph.D./Charles R. Bonapace, Pharm.D.
CDTL Review	Janice Brown, M.S.

OND=Office of New Drugs
OMP=Office of Medical Policy
OSE= Office of Surveillance and Epidemiology
OPDP=Office of Prescription Drug Promotion
OMEPRM=Office of Medication Error Prevention and Risk Management
DMPP=Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
OSIS=Office of Study Integrity and Surveillance
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Deferiprone is a small molecule iron chelator that was approved in 500 mg tablet form on Octeober 14, 2011 "for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate" (NDA 21825). The current application is for Ferriprox (deferiprone) oral solution, submitted as a 505(b)(1) NDA with no change in the indication.

2. Background

Available treatments of patients with transfusional iron overload due to thalassemia syndromes are:

- Deferoxamine (Desferal®, Novartis Pharmaceuticals) powder for Injection Solution (NDA 16267) approved on April 1, 1968
- Deferasirox (Exjade®, Novartis Pharmaceuticals) tablets (NDA 21882) approved on November 2, 2005
- Deferiprone (Ferriprox®, ApoPharma) film-coated tablets (NDA 21825) approved on October 14, 2011
- Deferasirox (Jadenu®, Novartis Pharmaceuticals) film-coated tablets (NDA 206910) approved on March 30, 2015.

Since treatment of patients may start as early as 2 years of age (as in the indications for both formulations of deferasirox) and compliance with the drug regimens have been problematic for all of the above products, there is a need for a more acceptable formulation than the available tablets. This new formulation of Ferriprox, a 100 mg/mL oral solution was developed for patients who have difficulty taking the tablets.

The application contains CMC information for the oral solution and demonstration of bioequivalence of Ferriprox 100 mg/mL oral solution with the 500 mg tablet. A new NDA is submitted instead of a sNDA, since this is a new dosage form of deferiprone.

3. CMC/Device

The applicant cross-referenced the CMC information for deferiprone to DMF (b) (4). It was reviewed and was found to be adequate to support NDA 208030. Stability data of drug substance supports a retest period of (b) (4) months.

Ferriprox oral solution contains deferiprone (100 mg/mL), hydroxyethyl cellulose, glycerin, purified water, HCl, artificial cherry flavor, peppermint oil, and FD&C Yellow No. 6. The commercial production batch size is (b) (4) Ferriprox oral solution is manufactured by (b) (4) into 500 mL amber polyethylene terephthalate round bottle and closed with a white polypropylene child-resistant cap with a foam liner. The nominal fill volume is (b) (4) mL. An expiration dating period of 18 months is granted for Ferriprox oral solution when stored at 20° to 25°C, protected from light. No product quality issues which preclude approval were found and the product quality review recommended approval of the NDA. No microbiology issues that preclude approval were found and the Microbiology Review recommended approval of the NDA. No facility issues that preclude approval were found and the facility review recommended approval of the NDA.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted for this NDA submission. ApoPharma Inc. cross-referenced NDA 21825 for the pharmacology/toxicology studies for deferiprone. The nonclinical studies reviewed under NDA 21825 to support the initial approval of Ferriprox (deferiprone) provide sufficient information to support the use of Ferriprox (deferiprone) 100/mL oral solution for the same indication.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval

5. Clinical Pharmacology/Biopharmaceutics

The Sponsor submitted the results of relative bioavailability study of deferiprone oral solution and deferiprone 500 mg tablets. In study LA21-BA, the bioavailability of 3 x 500 mg tablets of Ferriprox relative to that of 1500 mg deferiprone administered as the oral solution (15 mL, 100 mg/mL) was determined under fasting conditions in 41 healthy adult volunteers (28 males and 13 females).

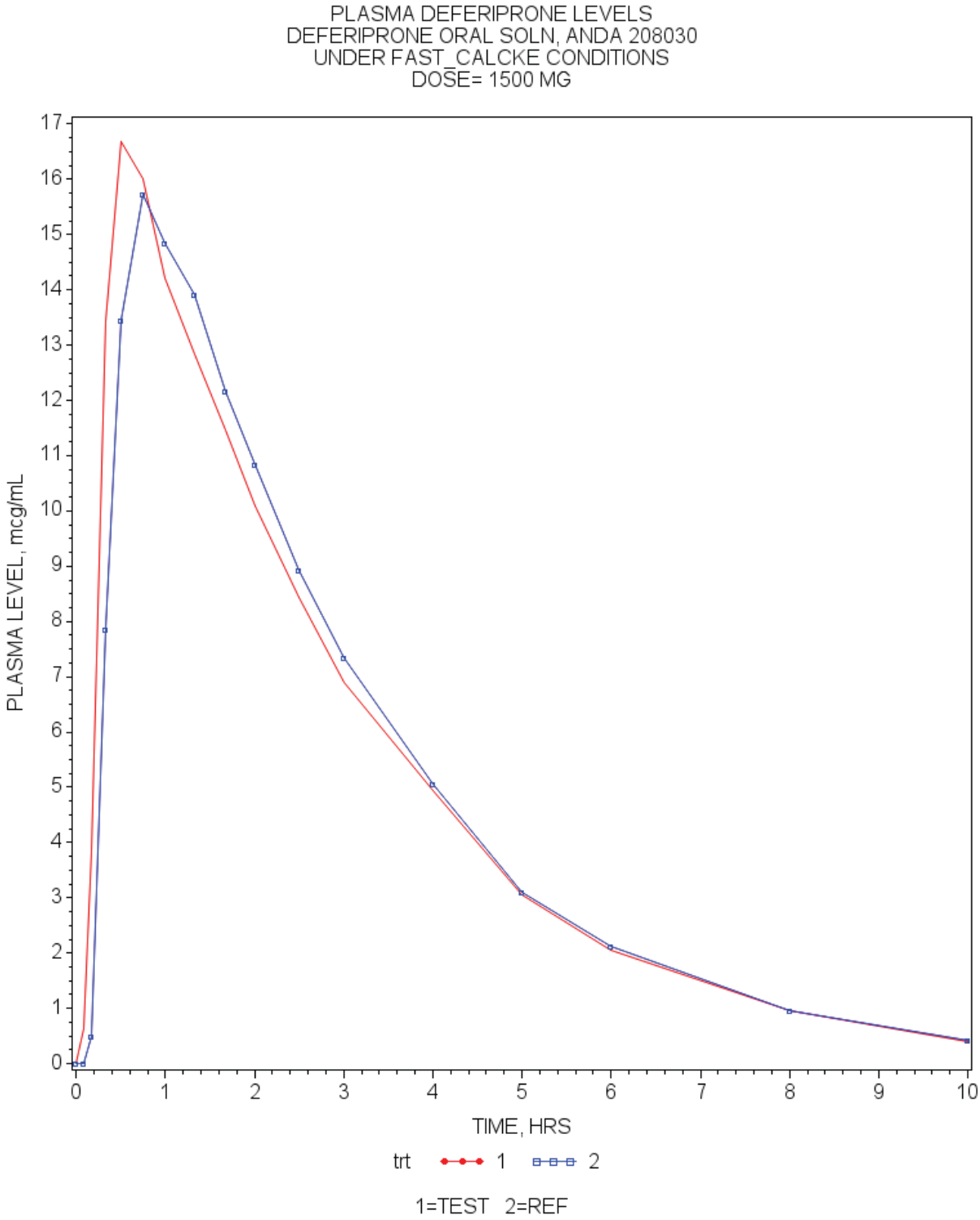
Study LA21-BE demonstrated that the relative bioavailability of ApoPharma's to-be-marketed deferiprone oral solution is comparable to the currently marketed Ferriprox 500 mg tablet, in that the primary PK parameters Cmax, AUC(0-t), and AUC(0-∞) for the test product demonstrated bioequivalence (BE) against the Ferriprox tablet (see Table 1 below).

Table 1: Summary Bioequivalence Statistics, Study LA21-BE (n=41)

Parameter (unit)	Least Squares Geometric Mean		Ratio of Test / Reference	90% Confidence Interval of Ratio
	Ferriprox Soln	Ferriprox®		
AUC0-t (h*ug/mL)	48.26	47.94	1.01	98.00 – 103.41
AUC0-∞ (h*ug/mL)	49.35	49.15	1.00	97.77 – 103.13
Cmax (ug/mL)	18.90	19.23	0.98	88.91-108.67

A graphical representation of deferiprone concentrations is shown below in Figure 1 below.

The clinical pharmacology reviewers concluded that the BE study demonstrated the bioequivalence of ApoPharm's deferiprone oral solution and Ferriprox® tablet.



I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

No new clinical information was submitted, besides the Bioequivalence study. The Clinical Reviewer concluded that no clinical issues that preclude approval were found and recommended accelerated approval for the same indications as the currently approved product Ferriprox tablets.

I concur with the conclusions reached by the clinical reviewers that there are no outstanding clinical issues that preclude approval.

8. Safety

The Clinical review for deferiprone oral solution evaluated the safety information from study LA21-BE. The review concluded "Review of safety in study LA21-BE …does not raise new or additional safety concerns for deferiprone oral solution formulation compared to the marketed deferiprone tablet product formulation. The safety labeling described in the deferiprone tablet product label is the same as the safety labeling for the proposed deferiprone oral solution product label."

9. Advisory Committee Meeting

This application was not presented at an Advisory Committee meeting.

10. Pediatrics

There is no Pediatric and Maternal Health Staff review for this NDA.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): N/A/
- Exclusivity or patent issues of concern: None.
- Debarment certification: Debarment certification was submitted by the Applicant and the US Agent in module 1.3.

- Financial disclosures: ApoPharma certified that they have not entered into any financial arrangement with the listed clinical investigator, Gaetano Morelli, M.D. Financial disclosure was submitted by the Applicant in module 1.3.
- Other GCP issues: None.
- DSI audits: No inspection was performed.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name, Ferriprox, was previously found acceptable during the review of NDA 21825 for Ferriprox (deferiprone) tablets
- Physician labeling, Medication Guide and Instructions for Use were reviewed by the clinical, non-clinical, clinical pharmacology, and product quality review teams, as well as by the reviewers from Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis. The review teams recommended changes to all sections of the applicant's proposed labeling, the Medication Guide and Instructions for Use. The applicant accepted the Agency's revisions.
- Carton and immediate container labels were reviewed by reviewers from the Division of Medication Error and Analysis. The Applicant accepted all suggested changes.
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13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval with no change in the indication.

- Risk Benefit Assessment: The clinical team continues to finds favorable benefit-risk profile for Ferriprox oral solution for the stated indication. This recommendation is based on the efficacy and safety of the marketed deferiprone tablet (Ferriprox) product and the available deferiprone supportive safety information from the bioavailability/bioequivalence study LA21-BE.

- Recommendation for Postmarketing Risk Management Activities: None.

- Recommendation for other Postmarketing Study Commitments: Postmarketing Requirements and Postmarketing Commitments which were issued during the accelerated approval of deferiprone tablets on October 14, 2011 also apply to deferiprone oral solution. In an August 20, 2015 submission, ApoPharma acknowledged the postmarketing requirements and commitments for Ferriprox (deferiprone) oral solution and agrees to the following milestone dates:

<u>Accelerated Approval</u>

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 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:	Completed.
Trial Completion:	02/2017
Final Report Submission:	07/2017

Postmarketing Requirements under 505(o)

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:	Completed
Annual Interim Report #1	04/2016
Annual Interim Report #2	04/2017
Annual Interim Report #3	04/2018
Study Completion:	10/2018
Final Report Submission:	04/2019

- Recommended Comments to Applicant: None.

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/s/

EDVARDAS KAMINSKAS
09/07/2015