

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208030Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	See electronic date stamp
<b>From</b>	Janice Brown, M.S.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	208030
<b>Applicant</b>	ApoPharma Inc.
<b>Date of Submission</b>	November 14, 2015
<b>PDUFA Goal Date</b>	September 17, 2015
<b>Proprietary Name / Established (USAN) names</b>	Ferriprox (deferiprone)
<b>Dosage forms / Strength</b>	Oral Solution 50 g/500 mL (100 mg/mL)
<b>Proposed Indication(s)</b>	For the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
<b>Recommended:</b>	<i>Accelerated Approval</i>

Include the following language in the approval letter:

An expiration dating period of 18 months is granted for Ferriprox (deferiprone) oral solution, when stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F), protected from light.

## 1. Introduction

Deferiprone is a small molecule, iron chelator approved for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The current application for Ferriprox (deferiprone) oral solution is submitted as a 505(b)(1) NDA.

## 2. Background

The subject of this NDA is a new formulation of Ferriprox, a 100 mg/mL oral solution, developed for patients who have difficulty taking the tablets. The approved therapeutic dose range of Ferriprox is 25-33 mg/kg three times daily and requires administration of a substantial number of tablets in most patients. Five milliliters of the solution provide the same dose of deferiprone as a single 500 mg tablet. The proposed indication for the oral solution is identical to that approved for the 500 mg tablets.

This NDA contains CMC information for the oral solution and demonstration of bioequivalence of Ferriprox 100 mg/mL oral solution with the 500 mg tablet. The applicant conducted a randomized, open label, comparative, two-way crossover bioavailability study (LA 21-BE) of Ferriprox oral solution and Ferriprox tablets under fasting conditions in 42 healthy subjects as the clinical basis to support the approval of the proposed drug product. The BE study results showed deferiprone oral solution and the tablets are bioequivalent. The applicant cross referenced NDA (b) (4) Ferriprox 500 mg film coated tablets, for the clinical safety and efficacy information and nonclinical studies for deferiprone. A new NDA is submitted instead of a supplement, since this is a new dosage form of deferiprone.

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

On December 12, 2001, deferiprone was granted orphan drug designation for the treatment of iron overload in patients with hematologic disorders requiring transfusion therapy. ApoPharma Inc. is claiming exemption from the Pediatric Research Equity Act (PREA) requirements for Ferriprox (deferiprone) 100 mg/mL oral solution.

## 3. CMC/Device

Drug Substance: The applicant cross-referenced the CMC information for deferiprone to DMF (b) (4). DMF (b) (4) was reviewed by Katherine Windsor, Ph.D. (final signature April 1, 2015) and was found adequate to support NDA 208030.

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4(1*H*)-one) is a bidentate iron chelator that preferentially binds trivalent iron cations (Fe<sup>3+</sup>) in a 3:1 (deferiprone:iron) complex.

Deferiprone is a white to pinkish white crystalline powder with a very bitter taste. Deferiprone is not hygroscopic since the drug substance stability data does not show an increase in moisture content over time. The drug substance is sufficiently soluble throughout the physiologically relevant pH range. Forced degradation studies demonstrate deferiprone in solution can degrade under basic conditions or upon excessive UV/Vis irradiation.

Stability data supports a retest period of (b) (4) months for deferiprone drug substance

(b) (4)

Drug Product and Process: Ferriprox oral solution is a clear, reddish orange solution. Each mL contains 100 mg deferiprone, hydroxyethyl cellulose, glycerin, purified water, hydrochloric acid, artificial cherry flavor, peppermint oil, FD&C Yellow No. 6, and sucralose. Each bottle contains 500 mL of Ferriprox oral solution.

The level of excipients were either within the FDA inactive ingredient database (hydroxyethyl cellulose, artificial cherry flavor, peppermint oil, and FD&C Yellow No. 6) or were found acceptable by the nonclinical reviewer (glycerol and sucralose).

The commercial production batch size is (b) (4). Ferriprox oral solution is manufactured (b) (4)

(b) (4)

The drug product is filled into a 500 mL amber polyethylene terephthalate (PET) round bottle and closed with a white polypropylene child-resistant cap with foam liner. The amber color of the PET bottles provides protection from light induced degradation. The nominal fill volume is (b) (4) with a tolerance volume of (b) (4). Filled bottles are labeled, security sealed, placed in a carton, and packaged. Each carton contains one filled, neck-banded and labelled bottle, one physicians insert, and one dosing cup.

An expiration dating period of 18 months is granted for Ferriprox oral solution, when stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F), protected from light.

The applicant proposed a (b) (4) month shelf-life for Ferriprox oral solution based on 24 months of long term stability data. At the 24 month test station, batches GT9874, GT9986, and GT9880 failed the USP antimicrobial effectiveness test acceptance criteria for the organism *Aspergillus niger*. Based on these failures, ApoPharma agreed to reduce the proposed shelf life to 18 months.

No product quality issues which preclude approval were found and the product quality review recommended approval of the NDA (Katherine Windsor, Ph.D., drug substance reviewer, final signature 25-Mar-2015, Donghao Lu, Ph.D., drug product reviewer, final signature 15-Jun-2015, Lin Qi, Ph.D., process reviewer, final signature 16-Jun-2015).

**Microbiology:** Ferriprox oral solution is microbiologically stable under simulated in-use conditions for 35 days after the container is opened for the first time. Data on antimicrobial effectiveness testing of Ferriprox oral solution stored in a close-bottle under long-term stability conditions ( $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65 \pm 5\% \text{RH}$ ) failed at the 24 month timepoint. Based on these microbiological failures, at the request of microbiology reviewer, ApoPharma agreed to reduce the proposed shelf life to 18 months.

There are no materials of biological origin or derived from biological sources used in the manufacture of the drug substance or drug product. No microbiology issues that preclude approval were found and the Microbiology Review (Denise A. Miller, Ph.D., final signature June 16, 2015) recommended approval of the NDA.

**Facility Review and Inspection:** The Office of Process and Facilities found no significant, outstanding manufacturing risks that prevent approval of this application. Based on the applicant's inspectional history and district file review, the manufacturing facilities for NDA 208030 are acceptable. No facility issues that preclude approval were found and the facility review (Zhong Li, Ph.D., final signature July 22, 2015) recommended approval of the NDA.

## 4. Nonclinical Pharmacology/Toxicology

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

The nonclinical reviewer has no concerns with the (b) (4) glycerol and the (b) (4) sucralose excipients used in the deferiprone oral solution at the defined levels. There are no new impurities in the Ferriprox 100 mg/mL oral solution and the acceptance criteria for impurities are consistent with those approved for the testing of the deferiprone drug substance used in the Ferriprox 500 mg tablets. No nonclinical issues that preclude approval were found and the Nonclinical Review (Brenda J Gehrke, Ph.D., final signature June 02, 2015) recommended approval of the NDA.

## 5. Clinical Pharmacology/Biopharmaceutics

To assess the relative bioavailability (BA) of ApoPharma's deferiprone oral solution, the Applicant submitted a study comparing pharmacokinetic (PK) of the oral solution against the marketed Ferriprox tablet (Study LA21-BE). The primary Clinical Pharmacology review conducted by Sriram Subramaniam, Ph.D. concluded, "This application is acceptable from a clinical pharmacology perspective. The Office of Clinical Pharmacology recommends approval of this NDA."

The following narrative is in part from the executive summary of the Clinical Pharmacology review of this submission.

ApoPharma conducted a clinical pharmacology study in healthy subjects in order to determine whether the proposed oral solution formulation is bioequivalent to the marketed tablet formulation. In study LA20-BA, the bioavailability of  $3 \times 500$  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.

Study LA21-BE demonstrated 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  $C_{max}$ ,  $AUC(0-t)$ , and  $AUC(0-\infty)$  for the test product demonstrated bioequivalence (BE) against the Ferriprox tablet.

The 90% confidence intervals of the test-to-reference ratios of the geometric means for  $C_{max}$ ,  $AUC(0-t)$ , and  $AUC(0-\infty)$  were within the acceptable BE limits of 80% to 125%. Therefore, the ApoPharma's to-be-marketed deferiprone oral solution and Ferriprox® tablets are bioequivalent.

**Safety** – Dr. Subramaniam concluded from a safety perspective, this study did not appear to demonstrate any substantial differences between the formulations with regard to related adverse events (AEs) or serious AEs. Following a 1500 mg dose, ten subjects (24%) had 26 AEs after administration of deferiprone solution and 6 subjects (14%) had 15 AEs after receiving deferiprone tablets.

Dr. Subramaniam emphasized a reliable safety assessment cannot be made in a single, dose cross over PK study due to the cross over study design and the short duration of study drug administration.

**Biopharmaceutics:** This NDA does not contain biopharmaceutics information. Banu Zolnik, Ph.D., Division of Biopharmaceutics in her review defers to the other disciplines for the approvability decision for this NDA.

## 6. Clinical Microbiology

There is no Clinical Microbiology review for this NDA.

## 7. Clinical/Statistical- Efficacy

The applicant cross referenced the safety and efficacy of deferiprone tablets in NDA 21825 to support the current NDA submission for deferiprone oral solution. The approval of the indication, "treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate" for deferiprone oral solution is supported by the efficacy results from study LA21-BE. The clinical reviewer, Dr. Dmytrijuk,

concluded “From a clinical perspective the bioavailability and bioequivalence appears to be similar for deferiprone oral solution compared to deferiprone tablets as demonstrated in the comparative bioavailability/bioequivalence study LA21-BE submitted in NDA 208030.” No clinical issues that preclude approval were found and the clinical review (Andrew Dmytrijuk M.D., final signature August 26, 2015) recommended accelerated approval for the same indications as the currently approved product Ferriprox® (NDA 21825; deferiprone tablets for oral use, i.e., deferiprone tablets) which was granted accelerated approval on October 14, 2011.

## **8. Safety**

This Clinical Review for deferiprone oral solution evaluated the safety information from study LA21-BE. Details of the LA21-BE study are described in section 5 (Clinical Pharmacology) in his review. Dr. Dmytrijuk’s review concluded “Review of safety in study LA21-BE supporting the deferiprone oral solution application NDA 208030 does not raise new or additional safety concerns for deferiprone oral solution formulation compared to the marketed deferiprone tablet product formulation. This study was conducted in normal healthy male and female subjects. The safety labeling described in the deferiprone tablet product label is the same the safety labeling for the proposed deferiprone oral solution product label.”

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting held for this application.

## **10. Pediatrics**

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

## **11. Other Relevant Regulatory Issues**

- Application Integrity Policy (AIP): Not applicable.
- 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 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. The Division of New Drug Bioequivalence Evaluation (DNDBE) accepted the clinical and bioanalytical data for NDA 208030, Study LA21-BE without an on-site inspection of the [REDACTED] (b) (4)
- Other discipline consults: None

## 12. Labeling

- **Proprietary name:** The proprietary name, Ferriprox, was previously found acceptable during the review of NDA 21825 for Ferriprox (deferiprone) tablets.
- The package insert (label), Medication Guide (MG) and Instructions for Use (IFU) have been reviewed by the clinical, clinical pharmacology, product quality and non-clinical reviewers, as well as by the Office of Prescription Drug Promotion (OPDP; Richard Lyght 8-Apr-2014), the Division of Medication Error Prevention and Analysis (DMEPA; Yelena Maslov). The review team has recommended changes to all sections of the sponsors proposed labeling. The review team's revisions were incorporated into the final label and sent to the applicant. The applicant has accepted the Agency's revisions.
- **Patient Labeling Team.** A patient labeling consult was requested to comment on the MG and IFU for Ferriprox (deferiprone) oral solution. A collaborative review by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) made a number of changes to the MG and IFU. The applicant accepted the recommended changes. DMPP and ODPD found the MG and IFU acceptable (Morgan A. Walker, final signature June 16, 2016 and James S. Dvorsky, final signature June 16, 2016).
- **OPDP/DDMAC.** The Office of Prescription Drug Promotion (OPDP) reviewed the draft labeling and did not have any comments for the package insert (see review by J.S. Dvorsky, June 2, 2015).
- **OSE/DMEPA.** The DMEPA review for container labels, carton and prescribing labeling, IFU, and MG by Michelle K. Rutledge was entered into DARRTS on June 15, 2015. DMEPA recommended a number of changes to the carton and container. The applicant accepted all the recommended changes.

## 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** Accelerated approval.
- **Risk Benefit Assessment:** The review of this NDA is based primarily on CMC and clinical pharmacology data. No clinical, CMC, clinical pharmacology, or nonclinical issues have

been found to preclude approval. The application has received an approve recommendation from the Office of Process and Facilities.

The clinical reviewer finds a favorable benefit-risk profile for Ferriprox oral solution for the indication: “treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.” This recommendation is based on the clinical review by Andrew Dmytrijuk, M.D., final signature August 26, 2015. Dr. Dmytrijuk’s recommendation is based on the safety and efficacy of the marketed deferiprone tablet (Ferriprox®) product (NDA 21825) and the available deferiprone supportive safety information from the bioavailability/bioequivalence study LA21-BE.

There are no outstanding regulatory issues for this NDA. This application may be approved.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies:** DHP concluded a REMS is not required for approval.
- **Recommendation for MedGuide:** DHP decided a MedGuide would be included with the labeling to ensure patients receive written advice about the risks of Ferriprox (deferiprone) oral solution.
- **Recommendation for other Postmarketing Requirements and Commitments:** Post-Marketing Commitments (PMCs) and Post-Marketing Requirements (PMRs) which were issued during the accelerated approval of deferiprone tablets on October 14, 2011 also apply to deferiprone oral solution. Only the PMCs and PMRs that have been fulfilled for deferiprone tablets can also be considered fulfilled for deferiprone oral solution. The remaining PMRs (PMR 1828-1 and PMR 1828-2) should be completed for deferiprone tablets in NDA 21825 and this NDA.

In an August 20, 2015 submission, ApoPharma acknowledged the post-marketing requirements and commitments for Ferriprox® (deferiprone) oral solution and agrees to the following milestone dates:

#### Accelerated Approval

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: 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

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

/s/  
-----

JANICE T BROWN  
08/27/2015