CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212269Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 24, 2020
From	Olanrewaju Okusanya, Pharm.D, MS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 212269
Applicant	ApoPharma Inc
Date of Submission	July 19, 2019
PDUFA Goal Date	May 19, 2020
Proprietary Name	Ferriprox
Established or Proper Name	Deferiprone
Dosage Form(s)	1000 mg film-coated tablets
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Applicant Proposed Dosing Regimen(s)	Deferiprone 25 to 33 mg/kg body weight, orally, two times a day for a total daily dose of 75 to 99 mg/kg body weight
Recommendation on Regulatory Action	Approval

1. Introduction

Deferiprone, an orally active iron chelator, was submitted as a new formulation to support a twice daily dosing regimen for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. This application cross-references NDA 21825 in which deferiprone (Ferriprox) was initially given accelerated approval on 10/14/2011.

2. Background

In the US, long term blood transfusion is one of the primary modes of treating patients with certain inherited anemias such as β-thalassemia and in some cases, sickle cell disease. Excess iron from blood transfusion circulates as a form of non-transferrin-bound iron (NTBI) or is deposited in tissues causing organ dysfunction through the overproduction of reactive oxygen species resulting in morbidity and often eventually mortality, mainly due to cardiac damage. Deferiprone, an orally active iron chelator initially approved in 2011, is one of the available options for the management of iron overload due to transfusions.

The approved dose is deferiprone 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to 99 mg/kg body weight. The applicant is proposing that the new formulation (b) (4) that allows for the twice daily administration of the total daily dose.

To support approval of this formulation, the applicant cross references NDA 21825 and conducted two bioequivalence studies comparing the rate and extent of deferiprone exposure in the new formulation to that in the currently approved formulation after single (Study LA53-0116) and multiple doses (LA45-0116) approved under NDA 21825. The results of these data are discussed under section 5 based on the review by Dr. Adeniyi. Tolerability studies (LA58-0117 and LA60-0118) were also conducted.

3. Product Quality

The product quality reviewers are shown below:

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Soumya Mitra	Ali Al Hakim
Drug Product	Amit Mitra	Anamitro Banerjee
Process/Facility	Zhijin Chen	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Amit Mitra	Anamitro Banerjee

The drug substance DMF was reviewed by Dr Mitra and it was found to be adequate to support the application with no product quality issues that would preclude approval.

Dr. McLamore, the Application Technical Lead (ADTL) review summarized the drug product and process with the following assessments:

Drug Product and Drug Process

The drug product, Ferriprox [redacted](b) (4) tablets is presented as a white to off-white, capsule shaped, beveled edge, biconvex coated tablets, engraved "FPX" score "DR" on one side and "APO" score "1000" on the other side. The drug product formulation includes hypromellose acetate succinate, magnesium oxide, colloidal silicon dioxide and magnesium stearate. The coating formulation [redacted](b) (4) includes triethyl citrate, [redacted](b) (4) talc, methacrylic acid copolymer [redacted](b) (4) All excipients used in the manufacture of the drug product are compendial, commonly used in [redacted](b) (4) oral dosage forms and demonstrate good compatibility with the drug substance.

NDA 212269 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 18-months.

Dr. McLamore, the Application Technical Lead (ADTL) review summarized the drug biopharmaceutics review as follows:

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability (2) the proposed tablet scoring/ alcohol dose dumping study and (3) bridging of the between the clinical and commercial formulations the evaluation of the need for bridging.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus I (Basket) at 100 rpm in 900 mL of 0.1N HCl (Acid Stage) and 0.05 M Phosphate Buffer, pH 6.8 (Buffer Stage) at 37°C. The proposed dissolution acceptance criteria are included in below:

Stage	Time	Acceptance Criteria	
		Whole	Half Tablets
Acid Stage:	120 mins (2 hrs)	(b) (4)	
Buffer Stage:	150 mins (2.5 hrs)		
	180 mins (3 hrs)		
	240 mins (4 hrs)		

The results of the dissolutions methods were determined to be adequate.

Tablet Scoring: The proposed tablet scoring did not result in dose dumping and was found acceptable based on the results from the BE study results. A slightly faster release dissolution profiles for the split tablets was expected and observed. These results support the proposed separate dissolution acceptance criteria for the half tablets.

Alcohol-Induced Dose-Dumping Potential: The study was conducted to evaluate the dose-dumping potential of the proposed drug product with alcohol consumption of. An in vitro study showed significant increases of deferiprone release at 2 hours to approximately (b) (4)% and of the label claim in the presence of 40% and approximately (b) (4)% of the label claim in the presence of 20% alcohol. The effect of 10% alcohol on drug release was negligible at 2 hours. This information was communicated to the appropriate review disciplines for labeling recommendations.

Bridging of the Clinical Formulations: With the exception of the (b) (4) coating top coat (b) (4) the Phase III tablets are identical to the proposed commercial product. (b) (4)

(b) (4) (b) (4) The applicant provided adequate dissolution data to support the bridging between the commercial composition and the composition used for the clinical batch. The data fully supports the bridging between the Phase III and proposed commercial product

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion were considered acceptable for batch release and stability testing for the drug products. Based on the dissolution profile comparison, the Biopharmaceutics review team concluded that bridging between of the Phase III product to the proposed commercial product is established. Accordingly, this application is recommended for approval from a biopharmaceutics perspective.

All facilities listed in NDA 212269 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 212269 is recommended for approval from a compliance perspective.

4. Nonclinical Pharmacology/Toxicology

Non-clinical pharmacology/toxicology data for this application were reviewed by Dr. Pedro Del Valle. The primary reviewer stated that nonclinical data were previously reviewed under NDA 21825 and/or NDA 208030 and that the review of additional nonclinical data was not needed.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology data for this application were reviewed by Dr. Adeniyi. To support the marketing of the new deferiprone formulation, Study LA53-0116 - a 4-period, 4-sequence, crossover study, comparing the PK of 1000 mg deferiprone DR under fasted and fed conditions to 1000 mg deferiprone IR under fed conditions and Study LA 45-0116 – a randomized, multiple-dose, 2-period, 2-sequence, crossover study conducted under fed conditions, were conducted to evaluate the bioavailability and bioequivalence of the two formulations.

The 2 formulations evaluated were shown to have similar exposure (GMR AUC (90% CI) either after a single dose (99.4 (97.1 - 102) or at steady state (99.0 (95.3 - 102)). Dr. Adeniyi found that the data provided by the applicant also supported the splitting of deferiprone tablets to make an appropriate dose to the nearest 500 mg and that the dosing of this new formulation twice daily was appropriate.

However, the applicant did not provide sufficient data (b) (4)
Dr. Adeniyi stated that

> "while the Cmax of the new deferiprone formulation is comparable to that of the IR formulation even when administered at a dose 1.5 times higher than the IR dose, the clinical impact of the lower the C_{max} is unknown as there have been no formal exposure-response analyses conducted with regard to safety or efficacy of deferiprone."

The clinical pharmacology reviewers stated that the data submitted in this application support the approvability of this application from the clinical pharmacology perspective (b) (4)

6. Clinical/Statistical- Efficacy

Clinical data submitted in this supplement was reviewed by the primary reviewer, Dr. Andrew Dmytrijuk and the secondary reviewer Dr. Kathy Robie-Suh. No new clinical information was submitted to support efficacy in NDA 212269. The sponsor cross references the safety and efficacy information for deferiprone in NDA 21825 for the deferiprone IR 500mg tablet formulation. Overall, the clinical review finding was that the application is acceptable from a clinical perspective.

7. Safety

Clinical safety data submitted in this application was reviewed by the primary reviewer, Dr. Andrew Dmytrijuk and the secondary reviewer Dr. Kathy Robie-Suh. In addition to the data provided in this NDA, the applicant cross-references the safety information for deferiprone in NDA 21825 for the IR deferiprone 500mg tablet formulation. Safety information from the following submissions submitted under NDA 21825 and NDA 208030 were also reviewed.

Dr. Dmytrijuk's assessment is reflected below

Reviewer comment for Section 7. In study LA45-0116 there were no deaths, SAEs, and all adverse events were reported to be mild or moderate severity. The most common AEs reported in ≥ 3 subjects was headache. Also, no new safety concerns were identified by this reviewer in Periodic Benefit-Risk Evaluation Reports and Annual Reports covering the period from September 1, 2018 to August 31, 2019 submitted under NDA 21825 or NDA 208030. Review of safety information from these submissions does not raise new or additional safety concerns for the deferiprone (b) (4) 1000mg tablet formulation compared to the marketed deferiprone IR tablet or oral solution formulations.

The safety labeling described in the deferiprone (b) (4) product label is the same as in the safety labeling for the proposed deferiprone IR tablet and oral solution product labels. It should be noted that the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for studies of deferiprone tablets under NDA 21825 and NDA 208030 should be completed and studies may be modified to allow use of the deferiprone (b) (4) R or oral solution formulations.

Overall, the clinical review finding was that the application is acceptable from a clinical perspective.

8. Advisory Committee Meeting

No Advisory Committee meeting was held for this supplement.

9. Pediatrics

Deferiprone has received orphan drug designation for the approved indication. No new pediatric data was submitted in this supplement.

10. Other Relevant Regulatory Issues

None

11. Labeling

Relevant recommendations for labeling were provided by the review teams during labeling meetings. As per the clinical pharmacology review, (b) (4) the "twice daily' dosing regimen was supported by the data. The Applicant submitted updated labeling (b) (4) While the new formulation has the same proprietary name as the currently approved product, the Applicant added a statement (b) (4) indicating the dosing frequency of the new formulation.

Given the differences in the dosing regimen, and the similarity in the proprietary name, the established name, and tablet strength, the following recommendations were provided to the applicant and detailed in DMEPA review memo (S. GRAW DARRTS 05/15/2020) to mitigate medication errors.

(b) (4)

(b) (4)

ii. Add the statement "NEW FORMULATION" on the principal display panel. The statement should be in bolded, red font and placed in a box to draw attention to this important information. For example:

(b) (4)

This statement can be added directly to the principal display panel label or can be achieved through a sticker. We recommend including this statement for approximately six months as patients are transitioned.

C. Comments for the Blister Pack

1. Revise the frequency of administration statement to "TWICE-A-DAY" in alignment with the recommendation for the 50-Count Bottle, 500-Count Bottle, and Carton Labeling.

D. Comments for the Currently Approved 1,000 mg Tablet Container Labels (NDA 021825)

To further differentiate the new twice-daily 1,000 mg tablet formulation from the currently approved three-times-daily 1,000 mg tablet formulation, we recommend adding a frequency of administration statement (i.e., THREE TIMES A DAY) to the principal display panel of the currently approved 1,000 mg tablet container label.

12. Post Marketing Recommendations

No new Post Marketing Requirements (PMR) and Commitments (PMC) are recommended for this application. We note that the applicant relies on and cross-references the safety and efficacy information under NDA 21825 for the deferiprone IR 500mg and 1000mg tablet formulations to support the application for deferiprone (b) (4) tablet formulation under NDA 212269 and that the indication remains under Accelerated Approval status.

The PMCs and PMRs issued with the approval of the deferiprone 500mg on October 14, 2011 under NDA 21825 should also apply to this application under NDA 212269. As such, the PMRs to 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 (PMR 1828-1) and to establish a registry in order to perform an enhanced pharmacovigilance study of agranulocytosis (PMR 1828-2), which remain ongoing, should be completed by the applicant. The use of this formulation in the trials to fulfil these deferiprone-related PMR are acceptable.

13. Recommended Comments to the Applicant

The sponsor has developed a new 1000 mg formulation of deferiprone. The application was acceptable for accelerated approval from the product quality, clinical, clinical pharmacology, biopharmaceutics, and pharmacology/toxicology perspective. Since all the disciplines conclude that the application is acceptable, the overall finding is an acceptable recommendation and therefore an approval letter should be issued.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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