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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208030
Supporting document/s:	1
Applicant's letter date:	November 17, 2014
CDER stamp date:	November 17, 2014
Product:	Ferriprox® (deferiprone) 100 mg/mL oral solution
Indication:	Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Applicant:	ApoPharma Inc.
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Brenda J Gehrke, PhD
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Kristopher Kolibab, PhD

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1 Executive Summary

1.1 Introduction

Ferriprox® (deferiprone) is an iron chelator approved for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The current deferiprone product is a 500 mg film-coated tablet. NDA 208030 has been submitted for a new Ferriprox (deferiprone) formulation consisting of a 100 mg/mL solution. To support the current NDA, ApoPharma Inc. is cross-referencing NDA 21825 for the pharmacology and toxicology studies of deferiprone.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies supporting the approval of deferiprone were reviewed under NDA 21825 by Dr. David Bailey (Reviews dated: June 27, 2007, August 4, 2008, and September 22, 2009). Prior to the approval of deferiprone in October 2011, a review by Dr. Haleh Saber (Dated October 8, 2011) contained a summary of the nonclinical studies and the recommended labeling. At the time of approval there were no nonclinical issues to preclude approval of Ferriprox (deferiprone) for the proposed indication considering the life-threatening nature of the disease and lack of adequate chelation therapy.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. 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 mg/mL oral solution for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

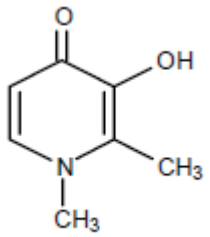
None

1.3.3 Labeling

The proposed labeling is consistent with the label for the current Ferriprox formulation. No new pharmacology or toxicology information was added to the proposed label.

2 Drug Information

2.1 Drug

CAS Registry Number	30652-11-0
Generic Name	Deferiprone
Code Names	APO-066
Chemical Name	3-hydroxy-1,2-dimethylpyridin-4-one
Molecular Formula/ Molecular Weight	$C_7H_9NO_2$/ 139.15 g/mol
Structure or Biochemical Description	
Pharmacologic class	Iron chelator

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 45724, NDA 21825

2.3 Drug Formulation

Ferriprox (deferiprone) 100 mg/mL oral solution is a clear, reddish orange solution with a peppermint and cherry-flavored (b) (4). Each bottle contains 500 mL of Ferriprox oral solution. The composition of the Ferriprox oral solution is provided in the table below. The 100 mg/mL solution contains (b) (4) glycerol. At the maximum total daily dose of 99 mg/kg Ferriprox, the total daily administration of glycerol would be (b) (4) for a 70 kg human and (b) (4) for a 90 kg human. The reported toxic dose low for oral administration of glycerol with toxicities of headache, and nausea or vomiting is 1.428 g/kg[1], resulting in a glycerol dose of (b) (4) for a 70 kg human and (b) (4) for a 90 kg human. This is a (b) (4) safety margin. Based on this information, the amount of glycerol in the Ferriprox 100 mg/mL solution is acceptable.

The 100 mg/mL solution of Ferriprox contains (b) (4) of sucralose as a (b) (4). Based on the maximum total daily dose of 99 mg/kg/day, a 70 kg human would be administered (b) (4) of the solution per day, which would result in (b) (4) of sucralose per day. The FDA's acceptable daily intake of sucralose in the diet is 5 mg/kg/day and results in an exposure of 350 mg/day sucralose for a 70 kg human. Therefore, the amount of (b) (4) sucralose in the 100 mg/mL solution of Ferriprox is (b) (4) times (b) (4) than FDA's daily limit for sucralose of 5 mg/kg/day. An information request was sent to the Applicant to provide a justification

[1] ToxNet search: http://chem.sis.nlm.nih.gov/chemidplus/rn/56-81-5

for the amount of sucralose in the 100 mg/mL solution product for Ferriprox. In the response provided on May 1, 2015, the Applicant explained that the Ferriprox 100 mg/mL oral solution was originally developed for the European market and the maximum acceptable daily intake of 15 mg/kg/day recommended by the European Regulatory Agency was used to establish the concentration of sucralose in the drug product. Based on the information provided, there are no pharmacology/toxicology concerns with the amount of sucralose in the Ferriprox 100 mg/mL solution.

Quantitative and qualitative composition of Ferriprox 100 mg/mL oral solution
(excerpted from Applicant's submission)

Component and Quality Standard (and Grade, if applicable)	Function	Strength:100 mg/mL		
		Quantity per bottle (500 mL fill size)	(b) (4)	% (w/v)
Deferiprone (In-house)	Active drug substance	50.00 g**		10.0
Hydroxyethyl cellulose (b) (4) (NF/EP/BP)	(b) (4)	(b) (4)		(b) (4)
Glycerin/Glycerol (USP/EP)				
Hydrochloric acid (NF/EP)				
Sucralose (NF/EP)				
Artificial cherry flavour (b) (4) (In-house)				
Peppermint oil (In-house)				
FD&C Yellow No. 6* (In-house)				
Purified water (USP/EP)				
Total	-	571.0 g (500 mL)		

(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

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 Ferripprox 500 mg tablets. There are no pharmacology/toxicology concerns with impurities at this time.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for Ferriprox® (deferiprone) oral solution is for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. This is the same indication approved for the current Ferriprox formulation (tablet). Deferiprone is administered orally at the recommended dose of 25 mg/kg to 33 mg/kg body weight three times per day for a total daily dose of 75 mg/kg to 99 mg/kg body weight.

2.7 Regulatory Background

Deferiprone was granted orphan drug designation for the treatment of iron overload in patients with hematologic disorders requiring transfusion therapy on December 12, 2001. Ferriprox was approved by the FDA on October 14, 2011 under NDA 21825. Under IND 45724, preliminary responses for a pre-NDA meeting scheduled with the FDA to discuss an NDA submission for the Ferriprox 100 mg/mL oral solution were sent to the Sponsor in July 2014 and the meeting was subsequently cancelled by the Sponsor. NDA 208030 was submitted on November 17, 2014.

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/s/

BRENDA J GEHRKE
06/02/2015

CHRISTOPHER M SHETH
06/02/2015