CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021825Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	21825
Applicant Name	ApoPharma, Inc.
Date of Submission	4/14/11
PDUFA Goal Date	10/14/11
Proprietary Name / Established (USAN) Name	Ferriprox/deferiprone
Dosage Forms / Strength	500 mg Tablet, immediate release
Agency Proposed Indication(s)	for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	George Shashaty, M.D./Kathy Robie-Suh, M.D., Ph.D.
Statistical Review	Qing Xu, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yash Chopra, PhD./Adebayo Laniyonu, Ph.D. and Haleh Saber, Ph.D.
CMC Review/OBP Review	W. Michael Adams, Ph.D./Janice Brown, Ph.D./Sarah Pope-Miksinski, Ph.D. Tien-Mien Chen, Ph.D./Angelica Dorantes, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Joseph Grillo, Ph.D./Julie Bullock, Ph.D.
DDMAC	James Dvorsky
DSI	Anthony Orencia, M.D./Tejashari Purohit Sheth, M.D./Leslie Ball, M.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	Loretta Holmes, BSN, PharmD/ Irene Z. Chan, PharmD, BCPS/Carol Holquist, RPh
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Pediatrics Maternal Health Team	Alyson Karesh, M.D./Hari C. Sachs, M.D./Lisa Mathis, M.D. Leyla Sahin, MD/ Karen Feibus, M.D./ Lisa Mathis, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Ferriprox is an oral formulation iron chelator. Apotex/ApoPharma Inc. initially submitted this New Drug Application (NDA) on December 21, 2006 under the Continuous Marketing Application program allowing for the submission of parts of the NDA as long as the parts consisted of Reviewable Units (RUs). The applicant proposed the application for *"the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy."* The first RU was the PharmTox unit which was submitted on December 21, 2006. The subsequent RUs were Chemistry, Manufacturing and Control, and Clinical Pharmacology units (submitted on September 26, 2007). The last combined Clinical and Statistical unit was submitted on January 29, 2009 which triggered the review clock. However, the application could not be approved during the first cycle due to the need to clarify clinical data issues, clinical pharmacology issues, chemistry, manufacturing and control issues, and a failed facility inspection. The applicant was sent a complete response (CR) letter on November 30, 2009. Following receipt of the CR letter, the applicant met with the Agency and submitted several proposals to address the clinical concerns outlined in the CR letter. The applicant responded to the complete response letter on April 14, 2011.

Deferiprone has been approved since 1999 in Europe. From the European Medicines Agency website:

The European Commission granted a marketing authorisation valid throughout the European Union for Ferriprox on 25 August 1999. The marketing authorisation holder is Apotex Europe B.V. The marketing authorisation is valid for an unlimited period.

The following is the language is from the therapeutic indication section:

Ferriprox is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

2. Background

Regulatory History

ApoPharma's April 14, 2011 submission is a complete response to the Agency's November 30, 2009 CR letter for the original NDA for deferiprone. The indication has been narrowed to for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate. The complete response addressed issues identified with the clinical data, clinical pharmacology data, chemistry, manufacturing and control, and a failed facility inspection. The major clinical issue concerned the pivotal trial. The clinical pharmacology issues included the lack of some needed

studies. The CMC issues were complicated and involved a failed site inspection, problems with a drug master file, and multiple process issues.

In the original submission, the sponsor provided as primary support for efficacy, data from a single, controlled trial (Study LA-16-0102). In this study, 61 adult patients with thalassemia were randomized to therapy with either deferiprone or deferoxamine. The primary efficacy measure was cardiac magnetic resonance imaging (MRI) T2* to assess cardiac iron burden. Secondary endpoints included changes in serum ferritin and liver iron concentration. The initial NDA submission received a Complete Response (CR) due to a number of deficiencies including the following clinical concerns: insufficiency of evidence for efficacy from adequate and well-controlled investigations; lack of sufficient information to establish the clinical meaningfulness (e.g., improved survival, symptoms, functional status or other clinical benefits) of incremental changes in cardiac MRI T2*, a major efficacy parameter in the clinical studies of deferiprone; and lack of data to verify absence of a mortality disadvantage when deferiprone is used over a long period of time. Recommendations to correct these and other deficiencies were provided to the sponsor in the CR letter.

Now the sponsor has submitted data from a prospective, planned multi-institutional study (LA36-0310) entitled “Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate” which consists of an analysis of data across multiple studies. The application also includes data from other clinical trials, some performed by the sponsor and others performed by independent investigators, as well as a number of publications related to the use of deferiprone.

Thalassemia
Patients with thalassemia have an inherited disorder characterized by defective synthesis of subunits of hemoglobin (Hgb) with resulting decreased Hgb production and reduced red blood cell survival. The clinical manifestations of the disorder can be diverse and vary from an absence of symptoms to profound fatal anemias in utero or in early childhood. Treatment for the more severe forms of the disease includes red blood cell transfusions, iron chelation therapy and allogeneic bone marrow transplantation.

Patients with thalassemia also have increased iron absorption in the gastrointestinal tract. One basic clinical problem for patients with thalassemia syndromes requiring transfusions is that these patients develop iron overload because of an inability to remove the excess iron. The excess iron accumulates as a result of transfusions and the increased gastrointestinal absorption. Since the body cannot get rid of the excess iron, the iron deposits in tissues such as the liver and heart and endocrine glands disrupting normal function. Excessive accumulation in the heart can lead to cardiac failure and arrhythmias leading to death.

The treatment for excess iron is chelation therapy. An iron chelator binds to iron in the blood or organs of deposition with the subsequent excretion of the bound complex in

the urine or feces. The first drug approved for iron chelation, Desferal (deferoxamine), was approved for use in 1968. However, not all patients can tolerate deferoxamine because of side effects and difficulties with its administration (the need for subcutaneous or intramuscular infusion with the use of a pump over 10-12 hours 5 of 7 days each week). In 2005, Exjade (deferasirox), an orally administered agent, was granted accelerated approval for use as an iron chelator.

Consistent with the Guidance for Industry on Available Therapy, only deferoxamine can be considered available therapy.

3. CMC/Device

Drs. Adams, Brown, and Pope-Miksinski reviewed this NDA. From the primary CMC review:

From a CMC standpoint, this application is recommended for approval pending the receipt of an overall acceptable recommendation from the Office of Compliance. The submission is complete and all other CMC review issues have been resolved.

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).

Dissolution criteria are acceptable.

The Office of Compliance recommendation is acceptable.

4. Nonclinical Pharmacology/Toxicology

There are no issues which would preclude approval of deferiprone based on the pharmacology reviews. From the current Pharmacology/Toxicology Team Leader review:

Nonclinical studies needed in support of the proposed indication have been conducted and reviewed by the Agency. Deferiprone is considered genotoxic, carcinogenic, and teratogenic. It is recommended that this drug be used in a serious disease, when other therapies are considered inadequate. Women of reproductive potential should be advised to avoid pregnancy when taking Ferriprox. Based on the Indications and Usage of the label, Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. There are no nonclinical issues at this time to preclude approval of Ferriprox (deferiprone) for the proposed indication considering the life-threatening nature of the disease and lack of adequate chelation therapy.

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