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APPLICATION NUMBER:

021825Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD, Office Director
Subject	Office 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
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, M.D./ 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

1. Introduction

Apotex/ApoPharma Inc. submitted the complete New Drug Application (NDA) for deferiprone, an oral iron chelator, on January 29, 2009 for the proposed indication of *"treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy."* On November 30, 2009, a complete response letter was issued for this application due to clarifications needed for clinical data issues; clinical pharmacology issues; chemistry, manufacturing and control issues; and a failed facility inspection. The applicant responded to the complete response letter on April 14, 2011 addressing the major clinical issue of the pivotal trial; the clinical pharmacology issues including the lack of studies conducted; and the CMC issues which involved a failed site inspection, problems with a drug master file, and multiple process issues.

2. Background

In the original submission, the sponsor provided data from a single, controlled trial (Study LA-16-0102) as primary support for efficacy. 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 several deficiencies including 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.
With the current submission, in response to the CR letter, the sponsor 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". 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.

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 (e.g., subcutaneous or intramuscular infusion via pump over 10-12 hours 5 of 7 days each week). In 2005, Exjade (deferasirox) was granted accelerated approval for use as an iron chelator.

Consistent with our *Guidance for Industry: Available Therapy* (July 2004), only deferoxamine can be considered available therapy.

Deferiprone has been approved in Europe since 1999.

3. CMC/Device

There are no outstanding CMC issues that would preclude approval.

The CMC review team granted a 24-month expiry for deferiprone when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).

4. Nonclinical Pharmacology/Toxicology

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

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.

5. Clinical Pharmacology/Biopharmaceutics

There are no issues which would preclude approval from a clinical pharmacology perspective. However, the clinical pharmacology team recommends post-marketing requirements (PMRs) to conduct PK trials to assess deferiprone and its primary metabolite in patients with renal and hepatic impairment; TQT assessment; and a commitment (PMC) to conduct *in vitro* studies to determine the affect of UDP glucuronosyltransferase (UGT) inhibition and induction on the metabolism of deferiprone to evaluate the need for additional *in vivo* drug interaction trials

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The following text from Dr. Robie-Suh summarizes the clinical findings during the first cycle.

For the initial NDA submission the sponsor provided a single randomized controlled trial (Study LA16-0102) comparing the use of deferiprone versus the use of deferoxamine in removing excess cardiac iron in subjects with thalassemia major. The study used a primary efficacy endpoint that employed magnetic resonance imaging of the heart (cardiac MRI) with measurement of a parameter termed T2 (T2 star) to*

evaluate extent of iron overload and effectiveness of chelation therapy. The primary efficacy analysis of change in cardiac MRI T2 from baseline to 12 months showed a 3.9 msec increase in cardiac MRI T2* in the deferiprone treatment group (N=29) and 2.3 msec increase in the deferoxamine treatment group (N=32). The study did not find a significant correlation between change in cardiac MRI T2* and measures of cardiac function and there were no differences between treatments in change in liver iron concentration (LIC). A retrospective supportive study, LA 12-9907, evaluating occurrence of cardiac disease also was submitted... Safety concerns for the drug were agranulocytosis (which occurred in 1.7% of patients in the deferiprone clinical studies), hepatic toxicity, gastrointestinal adverse reactions, arthropathy, cardiac (a case of torsades de pointes), neurological, and miscellaneous reactions. Also, (based on non-clinical studies) deferiprone is genotoxic and teratogenic.*

As stated in Dr. Farrell's summary review, due to uncertainty about the clinical meaning of the observed millimeters of change in T2*, the sponsor received a Complete Response letter and the Agency recommended a prospective randomized trial. The sponsor decided to pursue an indication for those patients in whom current available chelation therapy was inadequate. The sponsor prospectively developed a protocol and statistical analysis plan to identify patients from their extensive database of clinical trials who had an inadequate response to prior iron chelation. The sponsor utilized an independent selection committee to identify the patients meeting the criteria for enrollment in the prospective trial (LA36-0310). Nearly all the patients enrolled in LA36-0310 had thalassemia.

From Dr. Shashaty's second cycle review:

Study LA36-0310 assessed the change in serum ferritin from baseline to the end of one year's treatment with deferiprone in patients (almost all with thalassemia) with transfusion related hemosiderosis who appeared to be unsuccessfully treated with other chelators (almost exclusively deferoxamine). Patients were considered to be unsuccessfully chelated if, despite the use of a chelator, they continued to have a serum ferritin in excess of 2,500 µg/L prior to the initiation of deferiprone therapy. Secondary endpoints analyzed included changes in cardiac magnetic resonance imaging (MRI) T2 in patients with a baseline MRI T2* of less than 20 msec, and changes in liver iron concentration (LIC) in patients with a baseline LIC of greater than 7 mg Fe/g dry weight (dw). These latter values were also considered to be consistent with unsuccessful treatment with an iron chelator.*

The patients were selected for inclusion in the Study LA36-0310 by an independent committee based on a review of all patients who had been previously enrolled in sponsor supported studies, almost all of which had been submitted to the original NDA. The committee selected patients for possible inclusion based on a pre-specified protocol. Inclusion required that the patient must have been receiving iron chelating therapy and that, despite such therapy, continued to have one or more measurements indicating a persistently elevated body iron burden as described above. All patients were screened from data provided by the sponsor and available in its database from previous trials. The independent committee had no knowledge of the outcomes of deferiprone treatment. After receiving the list of potential enrollees for the study from the independent committee, the sponsor's statistics facility examined the same database for patients who had had at least one post-baseline measurement of any of the primary or secondary endpoint assessments within one year of commencing treatment with deferiprone. These patients were then enrolled and analyzed for the primary and secondary endpoints.

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