

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021825Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

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

<b>Material Reviewed/Consulted</b>	
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 Lanionu, 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 Orenca, 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 (deferisirox), 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 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).*

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.*

## 5. Clinical Pharmacology/Biopharmaceutics

There are no issues which would preclude approval of deferiprone based on the clinical pharmacology reviews. However, the clinical pharmacology review team recommends the following post-marketing requirements and commitment from their second cycle review:

### Requirements/Commitment

1. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. The subjects enrolled in this trial do not necessarily need to be in the target population (e.g., patients with thalassemia or sickle cell disease), but should have demographics that represent this population (e.g., age, weight gender, race) to the extent possible. The applicant will submit the protocol to the agency prior to conduct of the trial for agreement with the trial design. The applicant will conduct this pharmacokinetic trial in a patient population with mild to severe hepatic insufficiency, according to the Child-Pugh classification.
2. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects renal impairment. The applicant should conduct this pharmacokinetic trial in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences large enough to warrant dosage adjustments for each level of impairment. The subjects enrolled in this trial do not necessarily need to be in the target population (e.g., patients with thalassemia or sickle cell disease), but should have demographics that represent this population (e.g., age, weight gender, race) to the extent possible. The applicant will submit the protocol to the agency prior to conduct of the trial for agreement with the trial design. The applicant will conduct this pharmacokinetic trial in a patient population with mild to severe renal insufficiency.
3. Conduct a TQT assessment
4. Conduct *in vitro* studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone. The results of the *in vitro* evaluations will determine the need for additional *in vivo* drug interaction trials.

## 6. Clinical Microbiology

Not applicable

## 7. Clinical/Statistical-Efficacy

I have read the first cycle clinical reviews from Drs. Rieves, Robie-Suh, and Shashaty. The following text from Dr. Robie-Suh nicely 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. Consultations were obtained from the Center for Devices and Radiological Health (CDRH) (S.S. Rajan, Ph.D.) and the Division of Medical Imaging and Hematology (Dr. M. Fedowitz, 4/15/2009) regarding the use of MRI for imaging cardiac iron and from the Division of Cardiovascular and Renal Products (DCRP) (Dr. S. Targum, 4/20/2009) regarding significance of measured changes in cardiac function parameters in the LA16-0102 study and these consultative reviews were considered in the clinical review of the application. 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.*

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. Success was defined as a decrease in serum ferritin of 20% or more, a decrease in LIC of 20% or more or an increase in MRI T2\* of 20% or more.*

*Seven hundred forty seven (747) subjects were evaluated by the independent committee for possible enrollment. Of these, 264 met the inclusion criteria for serum ferritin, 117 for LIC and 39 for MRI T2\* based on a review of the sponsor's database. The overall success rate for the serum ferritin endpoint was 52% (C.I., 45%, 58%), while those for the LIC and MRI T2\* were 42% (C.I., 33%, 51%) and 62% (C.I., 45%, 77%), respectively.*

From Dr. Robie-Suh's review:

*The sponsor's primary efficacy analysis is shown below:*

**Table 7.4.1-1 Overall success rate for serum ferritin – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	264	136 (52%)	(45%, 58%)

Source: [Appendix 12.1.9.2 Statistical Appendix 4.1](#)

A total of 136 (52%) of patients had a 20% or greater decrease in serum ferritin from baseline to end of study. Mean serum ferritin at study entry was 4416 µg/L. The mean change in serum ferritin in the study was a decrease of 962 µg/L and ranged from a decrease of 10385 µg/L to an increase of 10002 µg/L. Success rates for patients from the various studies ranged from 26% in Study LA12-9907 (which contributed 19 patients) to 100% in Study LA15-0002 (which contributed 18 patients). Based on the sponsor's definition of treatment success as 20% of patients achieving a 20% or greater decrease in serum ferritin, treatment success for the study was declared for the primary efficacy endpoint.

Because some patients (about 11%) had received deferoxamine as well as deferiprone during the deferiprone treatment period of the study, an analysis was performed excluding these patients. The results of this analysis are shown below.

**Table 7.4.1-5 Subgroup analysis for success rate for serum ferritin: Ferriprox Monotherapy – ITT population**

Number of patients	Success rate (N, %)	95% C.I.
236	118 (50%)	(43%, 57%)

Source: [Appendix 12.1.9.2 Statistical Appendix 7.7](#)

In this analysis, 118 of 236 patients (50%) achieved sponsor-defined treatment success. Additionally, because questions regarding data quality for one investigator site (Dr. Nancy Olivieri, Toronto, Canada) were raised regarding one of the studies (LA-01) [see the 11/30/09 CR letter], an analysis was performed further excluding all data from that study and all data from the other study (LA-03) to which that investigator had contributed. For that analysis 109 of 220 (50%) patients achieved treatment success.

Finally, because the patients in the pediatric study (LA30-0307) were treated with a deferiprone solution that is not the subject of this NDA, an additional analysis was conducting excluding those patients as well as patients who had received combination/concurrent therapy. In that analysis 99/197 (50%) of patients achieved treatment success for the primary efficacy endpoint.

Results of the secondary efficacy analyses for change in liver iron concentration (LIC) and change in cardiac MRI T2\* are shown in the following tables.

**Table 7.4.1-8 Overall success rate for LIC – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	117	49 (42%)	(33%, 51%)

Source: [Appendix 12.1.9.2 Statistical Appendix 5.1](#)

**Table 7.4.1-11 Overall success rate for cardiac MRI T2\* – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	39	24 (62%)	(45%, 77%)

Source: [Appendix 12.1.9.2 Statistical Appendix 6.1](#)

*The sponsor-defined success rate was 42% for LIC and 62% for cardiac MRI T2\*. The mean change in LIC was a decrease of 1.7 mg Fe/g dry weight and ranged from a decrease of 32.6 mg Fe/g dry weight to an increase of 14.5 mg Fe/g dry weight. The mean change in Cardiac MRI T2\* was an increase of 3.3 msec and ranged from a decrease of 2 msec to an increase of 12.7 msec.*

*It should be noted that while the populations for the primary and secondary efficacy analyses overlapped, the populations for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin. Among the patients enrolled in the study, 228 were evaluable for serum ferritin only, 68 were evaluable for LIC only, and 9 were evaluable for cardiac MRI T2\* only. Thirty-one (31) were evaluable for both serum ferritin and LIC, 12 for both serum ferritin and cardiac MRI T2\* and 25 for both LIC and cardiac MRI T2\*. Only 7 patients were included in the analysis populations for all three of the efficacy endpoints.*

I have read the clinical and statistical reviews regarding the demonstrations of efficacy for the indication.

Other sponsors have proposed prospectively planned pooling of trial data when seeking approval for hematologic indications (Mylotarg and Angoimax).

LA36-0310 enrolled patients with iron overload due to thalassemia whose current chelation therapy was inadequate. In the absence of effective therapy for these patients, the serum ferritin, liver iron concentration, and cardiac iron concentration would be expected to worsen not improve as excess iron would continue to accumulate and cannot be removed from the body. LA36-0310 is a baseline-controlled trial, where the patient's baseline result is compared to their result after being on therapy, and is an externally controlled trial [historical controlled trial (21 Code of Federal Regulations (CFR) 314.126 (b) 2(v)]. From 21 CFR 314.126 (b) (2):

*An adequate and well-controlled study has the following characteristics:*

*(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.*

*(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized: ...*

*(v) Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).*

LA36-0310's use of an external control allows comparison to a control and provides a quantitative assessment of drug effect. The use of a prospectively planned protocol and independent selection committee allowed an adequate selection of patients for the trial and minimized the possibility of bias. The use of a prospectively planned statistical analysis plan allowed an adequate assessment of drug effect. Thus this trial can be considered an adequate and well-controlled trial under the CFR and ICH E10 guidance for regulatory purposes.

The choice of the primary endpoint, 20% reduction in baseline serum ferritin over a year, was discussed at the Oncologic Drugs Advisory Committee meeting. The sponsor had proposed the 20% reduction based on their outside expert consultants. In the absence of effective therapy, the serum ferritin would not be expected to be reduced by 20% as excess iron would continue to accumulate and cannot be removed from the body. In the absence of effective therapy, the serum ferritin would be expected to increase.

The Accelerated Approval regulations (21 CFR 314.500 and 21 CR 601) apply to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy). LA36-0310 enrolled patients with transfusional iron overload due to thalassemia who were unresponsive to available therapy (deferoxamine) and demonstrated an effect on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity and thus meets criteria for accelerated approval.

One issue that has been raised in the scientific literature with this product is whether there is loss of effectiveness over time. Effectiveness can be monitored by routine clinical assessment of the patient's underlying condition (blood, liver and cardiac

function). If this loss occurs, other therapy including experimental should be considered for an individual patient.

## **8. Safety**

During the investigational and marketing of this product two prominent safety issues have been discussed. One is hepatic fibrosis and the other is agranulocytosis.

The scientific issue of progression or development of hepatic fibrosis with deferiprone use was first raised in a New England Journal of Medicine article in 1998. However, this finding has not been consistently observed in other published studies. Review of scientific literature reveals that hepatic fibrosis can be observed in the setting of thalassemia with iron overload and/or hepatitis C without use of deferiprone so determining causality in this patient population is difficult. Post-European Union approval, few cases of hepatotoxicity have been reported.

Agranulocytosis was seen in approximately 1.7% of patients treated with deferiprone. Thirteen patients have died as a result of sepsis associated with agranulocytosis. The development of agranulocytosis appears to be idiosyncratic. The labeling will discuss the recommendations for monitoring and recommendations for what should occur if a patient develops neutropenia. The sponsor will conduct a registry in an attempt to better characterize those patients at risk.

Other side effects include gastrointestinal adverse reactions (e.g., nausea, vomiting), chromaturia, arthropathy, and thrombocytopenia. One case of Torsades-de-Pointes was reported.

I concur with the conclusions of the clinical review team regarding the safety.

Any post-marketing concerns about long term toxicity such as hepatic fibrosis or any other safety issue can be addressed through mechanisms such as labeling, a registry or post-approval study.

## **9. Advisory Committee Meeting**

This product was discussed at an Oncologic Drugs Advisory Committee meeting on September 14, 2011. The Committee voted 10 (yes) to 2 (no) that the available clinical data demonstrate a favorable risk-benefit profile for deferiprone.

## **10. Pediatrics**

Although the sponsor has submitted some data from a trial conducted in pediatric patients with thalassemia, the sponsor does not have a pediatric-friendly formulation proposed for the US market. The sponsor does market a liquid formulation in Europe.

The sponsor has agreed to meet with the Agency to discuss the development of a pediatric formulation.

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

Maternal Health Team and Pediatrics were consulted and provided labeling recommendations which were incorporated into labeling.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

### Division of Scientific Investigation (DSI)

In January 2009, Apotex/ApoPharma initially submitted a New Drug Application for deferiprone as a first-line iron chelation therapy for approval. The clinical support for this application was based primarily on the main study, Study LA16-0102 which was a multicenter, randomized, open label, active control clinical trial comparing the use of deferiprone versus the use of deferoxamine. This study was conducted from 2003 to 2004. The clinical review team requested a Division of Scientific Investigation inspection of the LA16-0102 study as the main study as is typically done for new drug applications. The clinical review team also requested a "for cause" inspection of a clinical site from another study, LA-01, due to concerns about adverse event reporting particularly for hepatic toxicity. LA-01 was a tri-center, randomized, parallel-group trial which evaluated iron chelation by liver iron concentration. One group received deferoxamine and the other group received deferiprone. LA-01 was terminated prior to completion in 1996. There were other clinical trials submitted in the NDA for deferiprone.

The DSI inspection of LA16-0102, the main study did not reveal any significant issues and the data were considered reliable for regulatory use. Inspection of the sponsor in conjunction with LA-16-0102 also did not reveal significant issues related to sponsor conduct. The DSI inspection of LA-01 did not allow a definitive conclusion because of missing source documentation.

Trials, where source documentation are lacking, are problematic for the Agency to use because these data are considered incomplete. Since LA-01 was not the main study for a regulatory decision, since source data was not able to be found for all enrolled, since supportive data could be provided from the remaining other clinical trials, and since concerns regarding hepatic fibrosis could be addressed in other ways; we determined that the data from LA-01 were not crucial for efficacy or safety considerations.

Excluding data from the site where source documentation were not available did not change the overall conclusions regarding safety and effectiveness.

In the resubmission, the sponsor was also asked to address inspectional concerns in the 2009 complete response letter. The sponsor's response addressed the concerns. No additional concerns were raised after review of that data.

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

The labeling was reviewed by all disciplines and consultant staff.

## **13. Decision/Action/Risk Benefit Assessment**

- Recommended regulatory action

Accelerated Approval

I concur with the recommendation of the review staff that deferiprone should be approved and the indication should be restricted to those who were studied in the prospective planned analysis. Almost 95% of the enrolled patients had thalassemia. Few patients with diseases other than  $\beta$ -thalassemia syndromes such as sickle cell disease or myelodysplastic syndrome were enrolled in the main trial (LA36-0310). Therefore with such limited numbers of patients with other underlying diseases, a concrete assessment of efficacy and safety cannot be made for those patients. I concur with the findings of the statistical review team that the data are limited so this application at best supports accelerated approval. This approval will be subject to the requirement that the applicant study the product further, to verify and describe its clinical benefit.

- Risk Benefit Assessment

The risk benefit assessment suggests that oral deferiprone is effective for the treatment of patients with transfusional iron overload due to thalassemia syndromes who have had an inadequate response to available iron chelator therapy (deferoxamine). The primary endpoint was serum ferritin which is not an established surrogate for clinical benefit. The most serious side effect is agranulocytosis. The most common side effects include: gastrointestinal specifically nausea, vomiting, and arthropathy.

- Recommendation for Post marketing Risk Management Activities  
Routine post-marketing surveillance except for enhanced pharmacovigilance for agranulocytosis (see requirements and commitments below)
- Recommendation for other Post marketing Study Requirements/  
Commitment

Requirements (draft – for final language see action letter)

Conduct a trial in patients with transfusional iron overload/hemosiderosis due sickle cell disease (including sufficient numbers of patients with sickle cell disease) in whom current chelation is ineffective to be able to make a statement about efficacy and safety

Conduct a TQT trial per ICH E14

Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment.

Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects renal impairment.

Establish a pharmacovigilance registry

Commitment

Conduct *in vitro* studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone. The results of the *in vitro* evaluations will determine the need for additional *in vivo* drug interaction trials.

Submit results of the “Tanner” trial comparing the effects of deferoxamine alone to the combination of deferoxamine plus deferiprone in patients with thalassemia major, reported in the journal “Circulation” in 2007.  
Submit the clinical study report and complete, raw datasets and analysis programs

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/s/  
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ANN T FARRELL  
10/14/2011