CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021825Orig1s000

MEDICAL REVIEW(S)

M E M O R A N D U M

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

Date: September 20, 2011

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Hematology Products
Office of Hematology and Oncology Products

Subject: Medical Team Leader Secondary Clinical Review
Ferriprox (deferiprone), resubmission received 4/14/2011; amended study report received 7/25/2011

To: NDA 21-825

Ferriprox (deferiprone) is an orally active iron chelator developed for use in treating iron overload. This is the second review cycle for this product. The NDA was initially submitted 1/29/2009 for the indication, "treatment of iron overload in patients with transfusion-dependent thalassemia and for treatment in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate". A complete response (CR) letter was issued on 11/30/2009. The current resubmission (received 4/14/2011) seeks approval of deferiprone for the indication: "for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate." The proposed dose is Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b) (4) mg/kg body weight.

Background

Patients with certain inherited anemias (importantly β-thalassemia and increasingly sickle cell disease in the U.S.) require frequent transfusion of red blood cells beginning at a young age to offset anemia that occurs because of inability to manufacture normal hemoglobin. Normal dietary absorption is about 1 mg daily which maintains a total body iron of approximately 3 to 5 grams in adults. One unit of packed red blood cells contains about 200 mg of iron. Because the body has no physiologic mechanism to excrete excess iron, repeated red blood cell transfusions over time result in massive iron overload. The excess iron becomes deposited in tissues and causes tissue damage due to iron-catalyzed peroxidation of membrane lipids and leads to morbidity and often eventually mortality, mainly due to cardiac damage. The liver and endocrine organs also are notably affected. Assessment of liver iron content (LIC) has been the generally accepted standard for

assessment of body iron burden; however, serum ferritin, a nonspecific parameter, is commonly followed clinically.

Currently available treatment options for management of iron overload due to transfusions include Desferal (deferoxamine mesylate), an injectable iron chelator approved in 1968 and Exjade (deferasirox), an orally active iron chelator approved in 2005.

Deferiprone binds iron in a 3:1 complex which is then excreted in the urine. The drug was first administered to humans in 1987, was approved in the European Union in 1999 and currently is approved in 61 countries, mostly for the indication of the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate. The U.S. IND for deferiprone (IND 45724) was opened 7/15/1994. Orphan Drug designation was granted on 12/12/2001 and Fast track designation was granted 1/26/2004. The fact that the drug was granted Fast Track designation reflects the serious nature of the condition for which the drug is intended to be used and the fact that at the time the designation was granted the only therapeutic option for these patients was deferoxamine which must be administered via continuous subcutaneous infusion over many hours each day and which, therefore, is difficult for many patients to comply with and/or tolerate.

For detailed background please refer to Dr. George Shashaty's Clinical Review (10/19/2009) and my Cross-Disciplinary Team Leader (CDTL) review (11/25/2009; addendum 12/31/2009) of the first cycle NDA submission.

Complete Response (CR) Letter
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., dated 7/26/2009 [signed hard copy 11/4/2009]) and the Division of Medical Imaging and Hematology (Dr. M. Fedowitz, 4/15/2009 [signed 4/28/2009]) 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.

Clinical deficiencies listed in the 11/30/2009 CR letter and information needed to address the concerns were as follows:

1. The application contains insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling and lacks substantial evidence of efficacy from adequate and well-controlled investigations. Listed below are our requests for additional data, followed by a summary of the basis for these requests.

2. A decrease in the cardiac content of iron, as measured by magnetic resonance imaging (MRI) T2* alterations, was the proposed treatment effect in the single confirmatory study intended to verify deferiprone safety and efficacy. Listed below are requests for additional information if you use this endpoint in any future regulatory submissions:
   a. Supply data from at least one additional prospective, randomized, controlled clinical study that verifies the proposed deferiprone treatment effect.

   b. Supply data that verify the clinical meaningfulness (e.g., improved survival, symptoms, functional status or other clinical benefits) of incremental changes in cardiac MRI T2* values. These data should establish the minimum millisecond increase in T2* that is indicative of a clinical benefit.

   c. In developing subsequent clinical studies, we encourage you to enroll pediatric patients with transfusional hemosiderosis. Data within the submitted confirmatory study were obtained entirely from adult patients.

3. Submit data that verify the absence of a mortality disadvantage when deferiprone is administered over a prolonged time period. These data could be obtained from follow-up survival information for all patients enrolled in Study LA-01 ("Randomized Trial of Deferiprone and Deferoxamine in Thalassemia Major") and Study LA-16-0102 ("Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients"). Alternatively, supply data from other randomized, controlled studies that allow an assessment of survival in comparison to a clinically appropriate control therapy. The need for survival data cannot be addressed by the submission of uncontrolled study data or data from historically controlled/observational-type studies.

4. Submit data that more thoroughly assess the arrhythmogenic potential of deferiprone. In addition to any other information, supply data from an assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers.

5. FDA inspectional findings could not fully verify the accuracy of data submitted by you for Study LA-01, with respect to the Toronto, Canada clinical site. The principal investigator at that site was Dr. Nancy Olivieri. We understand that you terminated that study site in May 1996, prior to study completion. Our comments below pertain solely to data that was generated at that study site prior to the termination of the site. Supply information that addresses the items listed below:

   a. A Good Clinical Practice (GCP) inspection of Dr. Olivieri's data revealed discrepancies between superconducting quantum interference device (SQUID) values verified by source documents at the site in comparison to the data submitted to the NDA.

      Address these discrepancies.

   b. The GCP Inspection of Dr. Olivieri's data also revealed that the liver biopsy iron concentration values reported in the NDA listings as provided by you in 2.2.1 could not be verified by source documents, because the source documents were not available.

      Provide all source documents to support the iron content as measured by liver biopsy.

6. With regard to Study LA-01, there appear to be inconsistencies in your analyses of the data and the exclusion of certain subjects and data points from the analysis. Specifically:

   a. Per Data Listing 2.2.2 in the NDA, several iron concentration data points were excluded from analysis and the rationale for each exclusion was provided in this data listing. However, the rationale for exclusion was inconsistently applied in your analyses. For example, Subjects 42, 43, 51, and 55, had all of their iron concentration data excluded from analyses because "patient[s] did not complete 24 months of chelator therapy." However, Subjects 25, 34, 37, and 59, were included in your analyses (as provided in Data Listing 2.2.1) even though these subjects apparently did not receive 24 months of chelator therapy.

      Address this inconsistency.

   b. We also note that Table 12.2, Patient Listing of Discontinued Patients, includes information for subjects from Dr. Olivieri's site from 1997, which was after the study site was terminated. Therefore, you appear to have access to at least some data collected after termination of the site.

      Confirm that all relevant data in your possession at the time of NDA submission, regardless of whether those data were generated after termination of the study site, were included in the application.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.