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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD, Office Director
Subject	Office Director Summary Review
NDA/BLA #	21825
Supplement #	
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 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	
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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 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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.

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 second cycle 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 the data from one investigator site 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 another study (LA-03). 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.

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): 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).

As stated in Dr. Farrell's review, 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 September 14, 2011 Oncologic Drugs Advisory Committee (ODAC) meeting. The sponsor had proposed the 20% reduction based on their outside expert consultants. The ODAC members voted (10 to 2) supporting a favorable risk to benefit evaluation using the 20% reduction in serum ferritin as the primary endpoint.

The Accelerated Approval regulations (21 CFR Part 314, Subpart H) 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.

8. Safety

As stated in Dr. Farrell's Division Director Summary Review, during the investigation and foreign 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 paper published in the New England Journal of Medicine 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.

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

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

11. Other Relevant Regulatory Issues

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 8 additional 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 is 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 8 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.

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

- The revised indication differs from that originally sought by the applicant. The originally requested indication was for the "treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy." Our November 30, 2009, letter to the applicant rejecting approval of this indication did not address our requirements for approval of a more narrow indication. The approved indication is the following: "For the treatment of patients with transfusional iron overload due to thalassemia syndromes *when current chelation therapy is inadequate.*"
- We are approving this drug for the treatment of a subpopulation affected by a rare, serious, and life-threatening condition for which other available therapy is inadequate.¹ The indication is limited to thalassemia syndromes reflecting the population of patients studied in the submitted clinical trials. Labeling specifically states "Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias". The Sponsor has made a commitment to study the drug in patients with sickle cell anemia.

¹ By "other available therapy" we mean other drugs that have received regular approval for treatment of iron overload. This excludes drugs that have received accelerated approval, for which postapproval studies to verify and describe clinical benefit are still pending. Thus, deferoxamine is the only drug we consider "currently available" in this context.

- This approval is supported by an adequate and well controlled study. This approval is supported by a prospectively planned analysis of data from twelve trials. We have approved applications based on prospectively planned analysis of data from multiple trials for hematological indications (Mylotarg and Angiomax).
- The Agency has used single arm trials for the approval of many agents in the setting of serious and life-threatening diseases. The single-arm design of this submission (i.e., the absence of a randomized control arm) is appropriate when the endpoint is directly attributed to the drug introduced and cannot be attributed to chance alone or the natural history of the disease. For example, the endpoint of tumor size reduction (“response rate” in hematology/oncology trials) is used in single arm trials for accelerated approval since a reduction in size of the tumor by a pre-specified amount does not occur spontaneously or by a chance finding. A similar scenario exists for the endpoint of a decrease in serum ferritin by 20%. With the continued use of blood transfusions, a decrease in serum ferritin is attributed directly to the drug and would not occur due to chance alone or the natural history of the disease.
- When a single-arm trial demonstrates an outcome that would not occur spontaneously, the finding may provide substantial evidence of safety and effectiveness in support of approval even in the absence of a concurrent control. In addition, secondary endpoints studied in these trials (a decrease in hepatic iron and radiographic assessment of cardiac iron) provide supporting evidence of the effect of the drug in the iron overload states.
- As noted above, our regulations describe the characteristics of an adequate and well controlled study (21 CFR 314.126). These regulations acknowledge that historical controls (i.e., comparison of a test drug with experience derived from the adequately documented natural history of a disease) are appropriate in this indication.
- When a surrogate endpoint is used to support accelerated approval, it must be “reasonably likely to predict clinical benefit.” The accelerated approval regulations specifically acknowledge that endpoints used for accelerated approval may have a degree of uncertainty in relationship to the ultimate clinical outcome, hence requiring further study in post-approval clinical trials to confirm clinical benefit. A 20% decrease in serum ferritin is an appropriate degree of improvement for use in defining the primary endpoint, according to a consensus opinion among investigators and as agreed by ODAC by their supporting vote recommending approval (10 to 2). We reasonably conclude that a decline of 20% reflects a real treatment effect, rather than random fluctuation, a spontaneous change in the disease, a placebo effect, or biased observation.
- CDER’s Office of Scientific Investigations (OSI) inspected 2 studies included in NDA 21-825, study LA16-0102 and LA-01. Regarding study LA16-0102, OSI concluded that the data are reliable in support of NDA 21-825. Regarding study LA-01, OSI concluded that its inspection was inconclusive with respect to data regarding hepatic toxicity.

- The prospectively planned analysis on which our approval of NDA 21-825 relies is not affected by the inclusion or exclusion of data from studies LA-01 and LA-03. The prospectively planned analysis points to the same conclusion regarding the safety and effectiveness of deferiprone for its approved indication whether or not data from studies LA-01 and LA-03 are included.
- On September 14, 2011, the ODAC considered approval of NDA 21-825. ODAC voted 10-2 in favor of accelerated approval. Some ODAC members in favor of approval while emphasizing the importance of additional studies, as required under our accelerated approval framework.
- As with all Subpart H approvals supported by data showing an effect on a surrogate endpoint, the applicant is required to conduct postapproval studies to verify and describe clinical benefit in patients. This approval is contingent on the applicant's submission of a successful postapproval trial in which deferiprone is used to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Under Subpart H, we often accept postapproval confirmatory trials in a setting other than the approved indication. For example, in hematology/oncology indications where the accelerated approval trial may enroll a heavily pretreated and refractory population, the confirmatory trials may be conducted in a different stage of the disease or in a less heavily pre-treated population.
- Our accelerated approval framework in Subpart H does not require the use of validated surrogate endpoints. If a surrogate endpoint is validated (as with the association between reduced blood pressure and the risk of cardiovascular disease), a study showing an effect on that surrogate endpoint would support regular approval rather than accelerated approval. Under our Subpart H regulations, a surrogate endpoint must be "reasonably likely" to predict clinical benefit, and confirmatory studies are required because uncertainty is attached to that determination. A 20% decline in serum ferritin is reasonably likely to predict clinical benefit in this case and was corroborated by secondary endpoints including a decrease in liver iron and improvement in cardiac iron concentration.
- Regarding risks associated with deferiprone, the Agency is requiring a boxed warning on the drug's label concerning the risk of agranulocytosis and a Medication Guide for patients highlighting several risks. Additionally, we are requiring 4 postapproval safety studies enforceable under section 505(o) of the Food, Drug, and Cosmetic Act. Please see Section 8 (Safety) above regarding discussion of potential hepatotoxicity.
- Finally, our approval of deferiprone is consistent with initiatives to provide important flexibility in the approval of drugs that treat rare and serious diseases, in the interest of patients in whom available therapy is inadequate.
- Recommended regulatory action

Accelerated Approval

The benefits and risks of deferiprone were discussed in the Division Director's Summary Review, the CDTL Review, Clinical Review and the September 2011 ODAC. The review team found the risk-benefit assessment to be acceptable as did the ODAC. I concur with the recommendation of the review team that deferiprone should be approved and the indication should be restricted to those who were studied in the prospectively planned analysis.

- 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. The primary endpoint was serum ferritin, a surrogate endpoint that is reasonably likely to predict clinical benefit. This approval will be subject to the requirement that the applicant study the product further, to verify and describe its 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/ Commitments

See action letter for PMRs and PMCs. This NDA is being approved under Accelerated Approval, therefore, the sponsor is required to conduct confirmatory trials to be considered for full approval.

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/s/

TAMY E KIM
10/14/2011

RICHARD PAZDUR
10/14/2011