



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

October 12, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Richard Pazdur, M.D.
Director, Office of Hematology Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO22/Room 2212
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock and Dr. Pazdur:

These comments from Public Citizen's Health Research Group are being sent in response to New Drug Application (NDA) #021825, submitted by ApoPharma (a division of Apotex, Inc.) and considered by the Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee (ODAC) on September 14, 2011, for deferiprone (Ferriprox) for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate:

We strongly oppose FDA approval of ApoPharma's NDA for deferiprone for treatment of patients with transfusional iron overload when current chelation therapy is inadequate because the data presented by the sponsor in support of the NDA were grossly insufficient and fail to demonstrate that deferiprone is safe and effective in the intended patient population (i.e., any patient with transfusional iron overload), even under the standards permitted under FDA regulations at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses").

Initial NDA Submission

Deferiprone is an oral iron chelator with the chemical name 1,2-dimethyl-3-hydroxypyrid-4-one. It binds iron in a 3:1 (deferiprone:iron) complex that is subsequently excreted mainly in the urine.¹

ApoPharma initially submitted its NDA for deferiprone on January 29, 2009, for the following indication:²

For the treatment of iron overload due to transfusion in thalassemia patients and for patients with transfusion-dependent iron overload who had not responded to other iron chelator therapy.

As part of its evaluation of the initial NDA submission for deferiprone, the FDA's Division of Scientific Investigations (DSI) conducted a clinical inspection of study LA01 entitled "Randomized Trial of Deferiprone (L1, Ferriprox) and Deferoxamine (DFO) in Thalassemia Major." Study LA01, a non-pivotal clinical trial submitted in the NDA, was a multicenter, randomized, controlled study in subjects with thalassemia and iron overload comparing deferiprone to deferoxamine. The DSI inspection of this study was triggered by safety concerns raised by the primary investigator, Dr. Nancy Olivieri, about progressive hepatic fibrosis seen in subjects receiving deferiprone.

The DSI inspection report for study LA01 included the following key observation:³

The ORA field investigator compared the data listings prepared in the assignment to the field office against the data summaries prepared by Dr. Olivieri's clinical site. Per ORA field investigator, this "raised a number of questions regarding the Sponsor's criteria for inclusion and exclusion of data...." in the data listings with respect to hepatic iron concentration data. "...Specifically, **the sponsor's data set excludes in their entirety....29 of 64 treated subjects.**"

The amended excluded number by ORA field investigator was 23 of 63 treated subjects, provided to DSI on October 15, 2009. **The rationale for the exclusion of the data ... appears to have been inconsistently applied by the sponsor.** [emphasis added]

DSI's overall assessment of findings from its inspection of study LA01 and general recommendations were as follows:⁴

The inspection of Dr. Olivieri's site (1) **revealed some discrepancies in the hepatic iron concentrations between the sponsor's data listings and the documents at Dr. Olivieri's site, and where source documentation was available, Dr. Olivieri's data appeared to be reliable**, (2) **there were data that the sponsor excluded from the 24-month completer analyses, that may not have been appropriate for exclusion**, and (3) Dr. Olivieri did have documents

at her site that suggested increased hepatic iron and/or hepatic fibrosis with chronic deferiprone therapy, although DSI was not able to verify the source for these values, and, in some instances, the fibrosis may have been confounded by coexistent hepatitis C infection and/or baseline fibrosis....

In summary, the inspection of Dr. Olivieri's site was unable to conclusively address [the Division of Medical Imaging and Hematology Products' (DMIHP's)] concerns regarding hepatic toxicity and waning efficacy with chronic deferiprone therapy ... In order to address these concerns, DSI recommends that DMIHP consider requesting that sponsor: **(1) contract with an independent third party to obtain source documentation from subjects at Dr. Olivieri's site to evaluate allegations of hepatic fibrosis and waning efficacy, and/or (2) conduct an additional long-term efficacy and safety study of adequate and well-controlled clinical trial(s).** [emphasis added]

A meeting of the ODAC was scheduled for October 2009 to review the NDA submission for deferiprone, but this meeting was cancelled, presumably because of the significant concerns raised by DSI's inspection of study LA01.

On November 30, 2009, the FDA issued a complete response letter rejecting approval of the initial NDA for deferiprone for the following reasons:⁵

For that 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. Results of efficacy analyses across endpoints were inconsistent. **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. **Among the recommendations was that the sponsor should provide data from at least one additional prospective, randomized, controlled clinical study that verifies the proposed deferiprone treatment effect.** [emphasis added]

NDA Resubmission

The FDA subsequently acquiesced to pressure from ApoPharma and allowed the sponsor to (1) modify the indication statement to one in which deferiprone would be used as second-line, rather than first-line, therapy for transfusional iron overload; (2) disregard the agency's recommendation to conduct at least one additional prospective, randomized, controlled study; and (3) seek accelerated approval for the modified indication statement based solely on a single study — study LA36-0310 — that involved a post-hoc, retrospective analysis of data from a subset of subjects enrolled in the 12 previously conducted clinical trials of deferiprone that varied widely in their study designs.

Under the FDA regulations at 21 C.F.R. Part 314, Subpart H, “the FDA may grant marketing approval for a new drug product on the basis of **adequate and well-controlled clinical trials** establishing that the drug product has an effect on a surrogate endpoint that is likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity” [emphasis added]

Study LA36-0310 clearly fails to satisfy the requirements of 21 C.F.R. Part 314, Subpart H in two ways. First, given the design of the study, it clearly did not qualify as an “adequate and well-controlled clinical trial.” Second, the primary end point of the study — a decline in serum ferritin of at least 20% over a period of up to one year on deferiprone therapy in more than 20% of subjects⁶ — has not been validated as a surrogate end point that is likely to predict clinical benefit.

Furthermore, the resubmitted NDA provided scant and insufficient data regarding the safety and efficacy of deferiprone in subjects with transfusional iron overload due to non-thalassemia disorders. A total of 35 subjects with either myelodysplastic syndrome or sickle-cell disease received deferiprone in clinical trials, compared to 607 subjects with thalassemia. Of note, agranulocytosis occurred in 8/607 (1.3%) of subjects with thalassemia and 3/35 (8.6%) of subjects with other types of anemia requiring transfusion and leading to iron overload. The FDA also reported that there had been 13 deaths due to agranulocytosis in postmarketing experience in other countries, although there have been no such deaths since 2008, when the sponsor established an educational and observational program to alert patients and physicians to monitor blood counts weekly and to discontinue the use of deferiprone at the earliest indication of the development of neutropenia.⁷

On September 14, 2011, the FDA's ODAC met to consider the resubmitted NDA for deferiprone. During that meeting, the following exchange took place between Dr. Wyndham Wilson, ODAC chair, and Dr. Pazdur:⁸

Dr. Wilson: There has never been a drug approved on the accelerated pathway on retrospective data like that [provided in study LA36-0310]?

Dr. Pazdur: Not that I am aware of. I would like to point out, however, that this is a very particular situation, and one that I wanted to make sure doesn't establish a precedent.

Two ODAC members, Dr. William Kelly, professor of medical oncology and urology at Thomas Jefferson University, and Dr. Mikkael Sekeres, associate professor of medicine at the Cleveland Clinic Taussig Cancer Institute, made the following comments in explaining their votes against approval of deferiprone:⁸

Dr. Kelly: I looked at the data, and the data are very sparse. It's not the quality of data that we typically would like to see ... I think we don't have a good idea what the true risk-benefit ratio of this drug is.

Dr. Sekeres: I have great concern about retrospective data, the unclear definition of previous inadequate chelation and the safety of this drug in the U.S. population who would actually use it, which has not been established.

Another ODAC member, Dr. Susan Shurin, acting director of the National Heart, Lung, and Blood Institute, although voting for approval, noted the following:⁸

I think the data are inadequate for us to know how to optimally use this drug, and additional studies are desperately needed.

Dr. David G. Nathan, a professor of pediatrics and medicine at Harvard Medical School and an expert in transfusional iron overload, submitted the following written comments to the FDA opposing approval of the NDA for deferiprone:⁹

I wish to state my firm opposition to such a decision [to approve deferiprone] because deferiprone has never been subjected to an appropriate clinical trial, and there are serious doubts about its efficacy and concerns about its toxicity.

Though some colleagues in Europe seem to have made up their minds about this drug — I have very serious reservations and find that the manufacturers of the drug have handled its analysis with disregard for the science of clinical trials.

Since there is an adequate (albeit imperfect) oral iron chelator available to US patients that has undergone excellent clinical trials, I oppose the licensing of deferiprone until the company mounts a respectable clinical trial that persuades those of us who have devoted our careers to transfusion induced iron overload that the drug is efficacious and safe.

Conclusions

In conclusion, given the lack of data from adequate and well-controlled clinical trials demonstrating the safety and efficacy of deferiprone, as well as serious questions raised by DSI's inspection of study LA01 regarding the integrity of clinical trial data

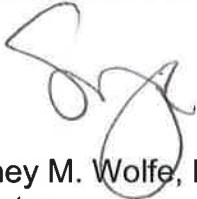
presented to the FDA by the sponsor, we urge the FDA to reject approval of NDA #021825 for deferiprone. Despite Dr. Pazdur's assertions to the contrary, FDA approval of deferiprone based on such inadequate data would indeed set a recklessly dangerous precedent for drugs reviewed under an accelerated approval process in the future.

Thank you for considering our comments in this very important matter.

Sincerely,



Michael Carome, M.D.
Deputy Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

¹ Food and Drug Administration. Briefing document for the Oncologic Drugs Advisory Committee meeting on September 14, 2011. Web page 4. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271537.pdf>. Accessed October 11, 2011.

² Food and Drug Administration. Briefing document for the Oncologic Drugs Advisory Committee meeting on September 14, 2011. Web page 2. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271537.pdf>. Accessed October 11, 2011.

³ Food and Drug Administration. Clinical inspection summary for NDA 21-825. October 27, 2009. Web page 12. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271571.pdf>. Accessed October 12, 2011.

⁴ Food and Drug Administration. Clinical inspection summary for NDA 21-825. October 27, 2009. Web pages 36-37. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271571.pdf>. Accessed October 12, 2011.

⁵ Food and Drug Administration. Briefing document for the Oncologic Drugs Advisory Committee meeting on September 14, 2011. Web page 2. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271537.pdf>. Accessed October 11, 2011.

⁶ Food and Drug Administration. Briefing document for the Oncologic Drugs Advisory Committee meeting on September 14, 2011. Web page 7. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271537.pdf>. Accessed October 11, 2011.

⁷ Food and Drug Administration. Briefing document for the Oncologic Drugs Advisory Committee meeting on September 14, 2011. Web page 31. Available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271537.pdf>. Accessed October 11, 2011.

⁸ Goldberg P. How low can you go? ODAC accepts retrospective study, data from Europe. *The Cancer Letter*. 2011;37:1-4.

⁹ Nathan DG. Written statement opposing approval of deferiprone. August 26, 2011. Available on web page 103 at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271676.pdf>. Accessed October 11, 2011.