Cooley's Anemia FOUNDATION

Leading the Fight Against Thalassemia

Citizen Petition

January 24, 2020

The undersigned submits this petition under 21 U.S.C. § 355(q) and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs and the Director for the Center for Drug Evaluation and Research to take action to require that businesses or companies providing the oral iron chelator deferiprone to U.S. patients with transfusional iron overload must follow appropriate steps to ensure sufficient patient safety.

A. Action Requested

Founded in 1954, the Cooley's Anemia Foundation(CAF) is the only national U.S. non-profit devoted exclusively to serving people with various forms of thalassemia, a rare genetic blood disorder also known as thalassemia. Our mission is to increase life expectancy and enhance the quality of life for those impacted by thalassemia. One way in which the Foundation fulfills its mission is by advocating on behalf of the thalassemia community on matters of key importance. It is for this reason that the Foundation is filing this Citizen Petition with the FDA concerning safe use of the oral iron chelator deferiprone, with specific concern about safety requirements for generic versions of the drug which may be forthcoming. CAF asks that the FDA require all products containing deferiprone be accompanied by a requirement to implement measures that will ensure a comparable level of monitoring and patient and physician support as is currently provided in the current Ferriprox voluntary REMS.

B. Statement of Grounds

Individuals born with severe forms of thalassemia require lifelong red blood cell transfusions as often as every two weeks. These frequent transfusions overload the body with iron, which must be removed before it destroys the heart, liver, pancreas and other organs. In order to remove the iron, an iron chelating drug must be administered. Deferiprone, marketed by ApoPharma under the brand name Ferriprox, is one of the iron chelators approved by the FDA for use in the United States. (The other FDA approved iron chelators are desferroxamine (brand name Desferal) and deferasirox (brand names Exjade and Jadenu.)

The FDA first issued an accelerated approval for Ferriprox (NDA No. 021825 (500 mg tablets) on October 14, 2011, "as an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate". Subsequently liquid formulations and a 1000 mg tablet were approved. Although it is not in the US label, the scientific literature is clear that Ferriprox has demonstrated superior iron removal from the heart compared to the other two iron chelators, making it the oral

product of choice for preventing iron-induced heart disease, the primary cause of early death in transfused thalassemia patients.

Even though the approval of Ferriprox has resulted in great benefit to transfused patients with thalassemia, its use is not without risks. According to the FDA label, deferiprone is genotoxic and carcinogenic, based upon studies conducted in animals. In some patients, it has a known effect to cause agranulocytosis, often preceded by a reduction in neutrophil counts. The risk of agranulocytosis, which makes patients more susceptible to infection, is of concern to the thalassemia community, although its apparent reversibility, upon stopping the medicine, is an important safeguard. For this reason, the Ferriprox label, which advises weekly blood counts to detect neutropenia, is considered important.

ApoPharma has implemented a voluntary REMS program, in which it contracts a third party to monitor physician and patient use of Ferriprox, including a system that regularly reminds prescribers and patients to conduct weekly neutrophil counts. Based on public documents and the experience of our patients, CAF's understanding of the ApoPharma voluntary REMS includes the following features:

i. Enrolling physicians and patients in a registry (which collects product use, side effects and neutrophil counts), requiring agreements to monitor neutrophil counts and to use birth control to prevent pregnancy.
ii. Dispensing only via a central pharmacy.
iii. Distributing only with safe-use conditions.
iv. Providing drug only on a monthly basis and only if needed.
v. Advising weekly blood draws to determine neutrophil counts, and more frequently if neutrophil counts become low or signs of infection appear.
vi. Advising the monthly measurement of serum concentrations of liver enzymes.
vii. Devising feedback loop with pharmacist/physician/patient to modify neutrophil monitoring if needed.
viii. Supplying support program, if blood levels/neutrophils counts are off or there are signs of infection.

ApoPharma also requires other services to ensure proper medication use and safety, including:

i. A mandatory special education program for physicians, pharmacists, and patients, requiring comprehension and adherence for admission into registries to prescribe, dispense or obtain product.
ii. Reinforcing safe-use conditions with quarterly communications.
iii. Periodic review of the voluntary REMS with reference to the registries and active pharmacovigilance for modifications to the voluntary REMS as needed.
iv. Engaging in active pharmacovigilance for drug use and adverse event monitoring, including tracking the potential for off-label use and associated risks.

We appreciate the establishment of this voluntary REMS program, in part, because it includes interaction with the patients upon each monthly refill, not only to enquire about adverse effects, compliance and other matters, but also to reinforce the need for weekly neutrophil counts. This constant reminder is a reassurance to CAF that our patient community can continue to receive the benefits of deferiprone, without undue risk, because of early detection of pending agranulocytosis.

Concern re: future monitoring

CAF is approaching the FDA now, because it has become aware that there is at least one generic applicant with an approval, referencing Ferriprox (Taro Pharmaceuticals, abbreviated new drug application No. 208800), although we do not know when there will be a launch, because the Orange book lists a patent for the use of deferiprone that expires in June 2021.

Based on available public information, it is unclear to CAF whether Taro or any other subsequent applicant would need to include the same level of safety monitoring as is employed by ApoPharma's voluntary REMS. CAF is concerned that without a REMS program in place (mandatory or voluntary) thalassemia patients will not be adequately monitored and patient infections and deaths might arise.

Specifically, CAF asks that the FDA require all products containing deferiprone be accompanied by a requirement to implement measures that will ensure a comparable level of monitoring and patient and physician support as is currently provided in the current Ferriprox voluntary REMS. We believe that this is crucial so that thalassemia patients who require this drug, especially those who need the cardiac benefits it supplies, can be assured that their health and safety will not be compromised. Only a requirement for measures comparable to those currently in place by ApoPharma can achieve this goal.

C. Environmental Impact

Petitioner is categorically excluded from this requirement.

D. Economic Impact

Economic impact information will be provided upon request of the commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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