Craig Butler
National Executive Director
Cooley's Anemia Foundation
330 Seventh Ave., Suite 200
New York, NY 10001

April 28, 2021

Re: Docket No. FDA-2020-P-0421

Dear Mr. Butler:

This letter responds to your citizen petition received January 24, 2020 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) 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 voluntarily by the application holder for Ferriprox (new drug application (NDA) 021825).

FDA has considered the information in your Petition, as well as other information available to the Agency. For the reasons set forth below, your Petition is denied.

I. BACKGROUND

A. Ferriprox

Ferriprox (deferiprone) was approved 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. It carries a boxed warning[1] stating that Ferriprox can cause agranulocytosis that can lead to serious infections and death, and that neutropenia may precede the development of agranulocytosis. The boxed warning advises measuring the absolute neutrophil count (ANC) before starting Ferriprox and weekly monitoring while taking Ferriprox. It warns that if infection develops, treatment with Ferriprox should be interrupted and the frequency of ANC monitoring should be increased. It also states that patients should be advised

[1]A boxed warning is ordinarily used to highlight for prescribers one of the following situations: (1) there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug, (2) there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug, or (3) FDA approved the drug with restrictions to ensure safe use because FDA the drug can be safely used only if distribution or use is restricted. See 21 CFR 201.57(c)(1) and FDA's Guidance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

to report immediately any signs of infection.[2]

B. REMS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) authorizes FDA to require a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that it is necessary to ensure that the benefits of the drug outweigh its risks. A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient package insert) to provide risk information to patients[3] and/or a communication plan to disseminate risk information to health care providers.[4] FDA may also require certain Elements to Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[5] The ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.[6] FDA can require a REMS at the time of initial approval of an NDA or after the drug has been approved if FDA becomes aware of new safety information[7] about a drug and determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[8]

A generic drug referencing a drug with a REMS will be subject to certain elements of the REMS for the listed drug (i.e., a Medication Guide requirement, packaging or disposal requirement, or ETASU).[9] A generic product is subject to those REMS elements only if the applicable listed drug is subject to a REMS. In other words, a generic product will not be subject to a REMS if the product it references does not have a REMS.

II. DISCUSSION

A. The Agency Determined That a REMS Was Not Necessary To Ensure That the Benefits of Ferriprox Outweigh Its Risks.

According to your Petition, the Ferriprox application holder, ApoPharma, has implemented a voluntary 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 (Petition at 2). You state that you appreciate the establishment of this voluntary program, in part because it "includes interaction with patients upon each monthly refill" and reinforces the need for weekly neutrophil counts (Petition at 2). You state that your

[2] Full prescribing information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021825s007lbl.pdf
[3] Section 505-1(e)(2) of the FD&C Act.
[4] Section 505-1(e)(3) of the FD&C Act.
[5] Section 505-1(f)(1) of the FD&C Act
[6] Section 505-l(f)(3) of the FD&C Act.
[7] Section 505-1(b)(3) of the FD&C Act.
[8] Section 505-1(a) of the FD&C Act.
[9] Section 505-1(i)(1) of the FD&C Act

organization is concerned that without a REMS program in place for generic products referencing Ferriprox, patients will not be adequately monitored (Petition at 3).

As stated above, a REMS will not be required of a generic product if one is not required of the drug it references. During the review of the application for Ferriprox, the Agency considered whether a REMS was necessary to ensure that the benefits of the drug outweighed the risks of agranulocytosis and neutropenia. Among other factors, the Agency considered that Ferriprox was likely to be prescribed by hematologists or other clinicians who are trained on how to monitor patients for, and have experience treating patients with, neutropenia and agranulocytosis. The Agency also considered that Ferriprox had a similar adverse reaction profile as the other marketed iron chelators (deferasirox and deferoxamine mesylate) which were not subject to a REMS. FDA concluded that labeling was sufficient to mitigate the risks, and additional requirements in the form of a REMS were not necessary.

B. No New Information Has Been Identified That Affects the Safety Profile of Ferriprox Since Approval in 2011.

The safety profile of Ferriprox has remained consistent in the 10 years since it was introduced in the United States. The Agency is not aware of, and the Petitioner has not provided new information that would change the Agency's conclusion that a REMS is not necessary to ensure the benefits outweigh the risks.

1. PMR Data

The impact of the voluntary risk mitigation measures that Petitioner notes are employed by ApoPharma cannot be quantified and do not support a determination that a REMS is necessary.

At the time of approval of Ferriprox, FDA issued several postmarketing requirements (PMRs) to the applicant, including PMR 1828-2 that required the applicant to establish a registry to perform an enhanced pharmacovigilance study of agranulocytosis during Ferriprox therapy and to collect blood samples for analysis to identify genetic factors that may indicate susceptibility to its occurrence. To fulfill this PMR, ApoPharma established a registry to collect complete clinical information about patients who develop agranulocytosis during deferiprone therapy.

As part of the PMR registry study, ApoPharma employed the following strategies:

- Controlled distribution of deferiprone through a centralized system with central oversight of dispensing
- Quarterly distribution of agranulocytosis reminders to prescribers and patients
- Distribution of a patient Medication Guide
- Distribution of a wallet card (as of May 2018)
- Routine pharmacovigilance, with enhanced case follow-up

The final PMR report provided a summary of registry results for enhanced pharmacovigilance of agranulocytosis associated with Ferriprox during the period December 5, 2011, through October 31, 2018. The rate of agranulocytosis in the United States registry was 1.24 per 100 patient-years, while the observed rate from foreign post-marketing sources was 0.18 events per 100

patient-years. The rate of agranulocytosis from foreign sources is based on spontaneous reporting, and thus likely represents under-reporting of the true incidence. By contrast, the US rate was developed from solicited reporting of the PMR-required registry and distribution was restricted to the registry pharmacy. Given these features of the US system for detection of agranulocytosis events, the US rate (1.24/100 person-years) is likely a reasonable estimate of the true incidence rate. This view is supported by the comparable rate observed from clinical trials (1.2 events per 100 patient-years).

We do not have any data to show the impact of the measures implemented in the PMR registry on prescribers or patients. For example, we have no data showing that prescribers received, read, understood, or acted on the communications they received. It is also unknown whether patients used the wallet card to seek medical care and, if they did, whether the wallet card was successful in assisting health care providers for patients seeking medical attention. Because the wallet card was not distributed until May 2018 (five months before the conclusion of the nearly 7 year registry period), the impact of this card on the safe use of Ferriprox throughout the registry period was likely minimal and likely did not contribute to the low incidence of agranulocytosis. The Agency has no information from which to conclude that these or other voluntary risk mitigation measures are necessary to ensure the benefits of Ferriprox outweigh its risks. The Agency determined that the PMR study did not identify any information that alters the benefit-risk balance of deferiprone.

2. FDA postmarketing surveillance

FDA reviewed the post marketing adverse event data in the FDA Adverse Event Reporting System (FAERS) for deferiprone as well as the published medical literature. The review did not identify any new safety signals for deferiprone and concluded that the reported adverse events are consistent with the known risks of agranulocytosis as described in labeling, and they did not identify increased severity or new risk factors.

The Petitioner has not presented new information. No new information was identified from the almost 7-year registry study that alters the safety profile of Ferriprox, nor is the Agency aware of any additional information suggesting that the safety profile has changed since the drug was approved in 2011. Therefore, the agency has determined that there is no need to require a REMS for Ferriprox at this time.

III. CONCLUSION

FDA determined that the benefits of Ferriprox outweigh its risks as labeled and that a REMS is not necessary. No new information has arisen to change that determination since Ferriprox was approved. Because a REMS is not required for Ferriprox, a REMS will not be required for any generic product referencing Ferriprox. Therefore, your Petition is denied. FDA will continue routine pharmacovigilance monitoring for deferiprone.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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