



NDA 216196

**NDA APPROVAL**

Agios Pharmaceuticals, Inc.  
Attention: Christina Baladi  
Associate Director, Regulatory Affairs  
88 Sidney Street  
Cambridge, MA 02139

Dear Ms. Baladi:

Please refer to your new drug application (NDA) dated and received June 17, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pyrukynd (mitapivat) tablets.

This NDA provides for the use of Pyrukynd (mitapivat) tablets for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at [FDA.gov](http://www.fda.gov).<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

---

<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 216196.**” Approval of this submission by FDA is not required before the labeling is used.

## **DATING PERIOD**

Based on the stability data submitted to date, the expiry dating period for Pyrukynd (mitapivat) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C.

## **ADVISORY COMMITTEE**

Your application for Pyrukynd was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the treatment of a disease.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of: 1) changes in reproductive hormones, changes in blood lipid levels, bone fractures and other adverse events

associated with long-term aromatase inhibition; and 2) increased systemic exposure of mitapivat in patients with hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

- 4178-1 Complete Trial AG-348-C-011, “An Open-Label, Multicenter, Extension Study of AG-348 in Adult Subjects With Pyruvate Kinase Deficiency Previously Enrolled in AG-348 Studies.” The final study report must include patient level data and a summary of all adverse events including changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

The timetable you submitted on January 31, 2022, states that you will conduct this trial according to the following schedule:

Trial Completion: 11/2024  
Final Report Submission: 06/2025

- 4178-2 Complete Trial AG-348-C-003, “A Phase 2, Open-Label, Randomized, Dose-Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency.” The final study report must include patient level data and a summary of all adverse events including changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

The timetable you submitted on January 31, 2022, states that you will conduct this trial according to the following schedule:

Trial Completion: 05/2025  
Final Report Submission: 12/2025

- 4178-3 Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of mitapivat in subjects with moderate (Child-Pugh B) hepatic impairment relative to adult healthy subjects, in accordance with the reduced study design described in FDA’s May 2003 Guidance for Industry – “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.” Submit subject-level datasets with the final report. Based on the results of this trial, additional subjects with mild (Child-Pugh A) and/or severe (Child-Pugh C) hepatic impairment may be enrolled.

The timetable you submitted on January 31, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2022  
Final Protocol Submission: 09/2022  
Trial Completion: 08/2023  
Final Report Submission: 03/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>3</sup>

Submit clinical protocol(s) to your IND 119825 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

---

<sup>4</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

*Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*<sup>4</sup>

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.<sup>5</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>6</sup>

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

**POST APPROVAL FEEDBACK MEETING**

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, MD, MMSc  
Director  
Office of Cardiology, Hematology,  
Endocrinology, and Nephrology  
Center for Drug Evaluation and Research

**ENCLOSURES:**

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

---

<sup>4</sup> For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>6</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

HYLTON V JOFFE  
02/17/2022 01:38:13 PM