



NDA 211349

**NDA APPROVAL**

Astellas Pharma US, Inc.  
Attention: Tim Farber  
Director, Regulatory Affairs  
1 Astellas Way  
Northbrook, IL 60062

Dear Mr. Farber:

Please refer to your New Drug Application (NDA) dated March 29, 2018, received March 29, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XOSPATA<sup>®</sup> (gilteritinib) tablets, 40 mg.

This new drug application provides for the use of XOSPATA (gilteritinib) tablets for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

### **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 text.

### **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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the carton and container labels submitted on August 9, 2018 (carton) and October 29, 2018 (container), 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 211349.**” Approval of this submission by FDA is not required before the labeling is used.

## **ADVISORY COMMITTEE**

Your application for XOSPATA was not referred to an FDA advisory committee because the safety profile is acceptable for treatment of patients with relapsed or refractory acute myeloid leukemia with a FLT3 mutation.

## **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 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 an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risks from long-term treatment with XOSPATA, to assess a known serious risk of differentiation syndrome, and to assess a signal of serious risk of ineffectiveness for patients having a mutation in the FLT3 tyrosine kinase domain.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

PMR 3542-1 Demonstrate safety of long-term treatment with gilteritinib. Submit an integrated report and the supporting data files to summarize the safety outcomes when all patients on 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 have completed at least three years of treatment with gilteritinib or withdrew earlier.

The timetable you submitted on November 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	02/2021
Final Report Submission:	02/2022

PMR 3542-2 Characterize the risk of differentiation syndrome in patients receiving gilteritinib for treatment of acute myeloid leukemia with a FLT3 mutation. Conduct a pooled analysis to characterize gilteritinib-related differentiation syndrome, specifically incidence, observed signs and symptoms, duration, and response to intervention based on patient-level data from on-going trials in patients with acute myeloid leukemia. Submit the study report and analysis data set.

The timetable you submitted on November 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission:	01/2019
Final Analysis Plan:	04/2019
Trial Completion:	10/2019
Final Report Submission:	04/2020

PMR 3542-3 Provide data to establish that the risks of gilteritinib are outweighed by the potential benefit for patients with AML having a mutation in the FLT3 tyrosine kinase domain (TKD). Submit a summary report and a supporting data set that includes outcomes for at least 30 patients with a FLT3-TKD mutation.

The timetable you submitted on November 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission:	01/2019
Final Analysis Plan Submission:	03/2019
Trial Completion:	04/2019
Final Report Submission:	05/2019

Submit clinical protocol(s) to your IND 117548 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.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

PMC 3542-4 Clarify the sensitivity of various FLT3 mutations other than internal tandem duplications (ITDs) and the D835Y tyrosine kinase domain mutation by in vitro testing. Include testing of I836 mutations, other D835 mutations, and other mutations reported to occur in AML. Submit a summary report.

The timetable you submitted on November 8, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2019

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”**

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

Information and Instructions for completing the form can be found at

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

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

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

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biological products 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, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD  
Director  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

### ENCLOSURE(S):

Content of Labeling  
Prescribing Information  
Patient Package Insert

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**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.**  
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/s/  
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ANN T FARRELL  
11/28/2018  
signing on behalf of Dr. Richard Pazdur