



NDA 210868

ACCELERATED APPROVAL

Pfizer, Inc.
Attn: Ann Carey
Senior Director, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Carey:

Please refer to your New Drug Application (NDA) dated December 5, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LORBRENA (lorlatinib) tablets, 25 mg and 100 mg.

We acknowledge receipt of your major amendment dated July 3, 2018, which extended the goal date by three months.

This new drug application provides for the use of LORBRENA (lorlatinib) tablets for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on:

- crizotinib and at least one other ALK inhibitor for metastatic disease; or
- alectinib as the first ALK inhibitor therapy for metastatic disease; or
- ceritinib as the first ALK inhibitor therapy for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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, text for the patient package insert) Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” 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 container labeling that are identical to the container labeling submitted on May 9, 2018, 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 210868.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for LORBRENA was not referred to an FDA advisory committee because this drug is not the first in its class, outside expertise was not necessary and there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 12, 2018. This requirement, along with required completion dates, is listed below.

3500-1	Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of lorlatinib in patients with
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locally advanced or metastatic non-small cell lung cancer without a history of prior systemic therapy for advanced disease and whose tumors harbor anaplastic lymphoma kinase (ALK) gene arrangement.

The timetable you submitted on September 12, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2016
Trial Completion:	12/2020
Final Report Submission:	09/2021

Submit clinical protocols to IND 118296.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each requirement 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.

Submit final reports to this NDA. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

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 an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of hepatic and renal toxicity.

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.

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

- 3500-2 Evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR agonists and non-PXR agonists) and non-CYP3A inducers (PXR agonists and non-PXR agonists) using a pharmacologically-relevant animal model capable of demonstrating the clinically observed hepatotoxicity signal. The study should be designed to inform the label regarding hepatotoxicity.

The timetable you submitted on June 20, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2019
Study Completion:	09/2019
Final Report Submission:	12/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of toxicity in patients with severe hepatic or renal impairment.

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

- 3500-3 Complete a pharmacokinetic trial to determine an appropriate dose of lorlatinib to minimize toxicity in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling” found at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm204959.pdf>

The timetable you submitted on May 17, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2018
Trial Completion:	05/2020
Final Report Submission:	01/2021

- 3500-4 Complete a pharmacokinetic trial to determine an appropriate dose of lorlatinib to minimize toxicity in patients with moderate and severe hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at

<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072123.pdf>

The timetable you submitted on May 17, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2018
Trial Completion:	03/2023
Final Report Submission:	02/2024

Submit clinical protocol(s) to your IND 118296 with a cross-reference letter to this 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).**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products 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>).

REPORTING REQUIREMENTS

We remind you that you must comply with the 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 biologics 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, please call the Regulatory Project Manager for this application within two weeks of receipt of this communication.

If you have any questions, call Shubhangi (Gina) Mehta, Regulatory Health Project Manager, at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
(Acting) Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

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/

GIDEON M BLUMENTHAL
11/02/2018