NDA 217188/S-08

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Pfizer, Inc.
Attention: Nestor Duci, MBA
Senior Manager, Global Regulatory Sciences
66 Hudson Boulevard East
New York, NY 10001

Dear Nestor Duci:

Please refer to your supplemental new drug application (sNDA) dated April 30, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Paxlovid (nirmatrelvir and ritonavir), co-packaged tablets.

This Prior Approval supplemental new drug application updates the U.S. Prescribing Information and Patient Information to include dosing recommendations in patients with severe renal impairment including those requiring hemodialysis based on data from Study C4671028. Additionally, the Section 12.4 (Microbiology) was updated with virology data.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 217188/S-08**." Approval of this submission by FDA is not required before the labeling is used.

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 none of these criteria apply to your supplemental application, you are exempt from this requirement.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] 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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated April 30, 2024, containing the final report for the following postmarketing requirement listed in the May 25, 2023 approval letter.

4392-6 Submit the final report with datasets for the ongoing trial, "A Phase 1, Open-Label, Non-Randomized Study To Investigate The Safety And PK Following Multiple Oral Doses Of PF-07321332 (Nirmatrelvir)/Ritonavir In Adult Participants With COVID-19 And Severe Renal Impairment Either On Hemodialysis Or Not On Hemodialysis" (Study C4671028; NCT05487040).

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the May 25, 2023 approval letter that are still open.

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-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

IMPURITY-RELATED CONSIDERATIONS

In addition please note that a nitrosamine drug substance-related impurity, (b) (4) also known as (b) (4) has been found in the manufactured batches of ritonavir used in PAXLOVID. FDA currently recommends an acceptable intake (AI) limit of (b) (4) ng/day for (b) (4) You may also pursue an AI limit different than the FDA-recommended limit with a scientifically justified rationale. FDA has issued guidance providing recommendations on the mitigation and control of nitrosamine impurities in human drug products.[6] Any changes to prevent or reduce (b) (4) in approved drug products must be reported to the Agency in accordance with 21 CFR 314.70.

Please note that it is your responsibility to ensure compliance with the FDCA and its implementing regulations, including addressing any potential product quality issues raised by the nitrosamine drug substance-related impurity noted above.

If you have any questions, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Wendy Carter, D.O.
Director
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research

[6] FDA guidance *Control of Nitrosamine Impurities in Human Drugs* (Sept. 2024, Rev. 2); *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (Aug. 2023); *CDER Nitrosamine Impurity Acceptable Intake Limits, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits.*

ENCLOSURES:

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

WENDY W CARTER
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