NDA 217188

NDA APPROVAL

Pfizer, Inc.
Attention: Karen C. Baker, MS
Senior Director
Pfizer Global Regulatory Sciences
66 Hudson Boulevard East
New York, NY 10001

Dear Ms. Baker:

Please refer to your new drug application (NDA) dated and received, June 29, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Paxlovid (nirmatrelvir tablets; ritonavir tablets), co-packaged.

We acknowledge receipt of your major amendments dated November 23 and December 5, 2022, which extended the goal date by three months.

This NDA provides for the use of Paxlovid (nirmatrelvir tablets; ritonavir tablets), co-packaged, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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

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

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.*[2]

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 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217188**." 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 Paxlovid (nirmatrelvir tablets; ritonavir tablets), co-packaged shall be 24 months from the date of manufacture when stored at room temperature.

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher (PRV), as provided under section 565A of the FDCA. This PRV has been assigned a tracking number, PRV NDA 217188. All correspondences related to this PRV should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This PRV may be transferred by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher. The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. FDA has published a draft guidance, *Material Threat Medical Countermeasure Priority Review*

[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.

Vouchers, at
https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm592548.pdf.
This guidance, when finalized, will represent the current thinking of the FDA on this topic.

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.

We are deferring submission of your pediatric studies from birth to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA is required postmarketing study. The status of this postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4392-1 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 6 to less than 18 years of age and weighing 20 kg or higher, with mild-to-moderate coronavirus disease 2019 (COVID-19).

Final Protocol Submission:	Completed
Study Completion:	07/2024
Final Report Submission:	12/2024

4392-2 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 2 to less than 6 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

Final Protocol Submission:	Completed
Study Completion:	04/2025
Final Report Submission:	10/2025

4392-3 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects from birth to less than 2 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

Final Protocol Submission:	Completed
Study Completion:	07/2026

Final Report Submission: 12/2026

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.[3]

Submit the protocol to your IND 153517, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 identify an unexpected serious risk of emergence and transmission of nirmatrelvir-resistant SARS-CoV-2 variants.

Furthermore, the active postmarket risk identification and analysis system as available 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:

4392-4 Conduct studies to characterize the phenotypic effects of the following amino acid substitutions on nirmatrelvir anti-SARS-CoV-2 activity: M^{pro} substitutions G11V, L30I, T45N, A94V, T98I/R/del, V104I, W207/R/del, F223L, H246Y; M^{pro} cleavage site substitutions A3571V, V3855I, A5328S/V, S6799A. M^{pro} substitutions can be evaluated in biochemical assays using recombinant M^{pro} proteins or cell culture assays using recombinant SARS-CoV-2 viruses or replicons. The M^{pro} cleavage site substitutions should be evaluated in cell culture assays using recombinant SARS-CoV-2 viruses or replicons.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2023
Study Completion:	12/2023
Final Report Submission:	01/2024

4392-5 Conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Conduct surveillance activities on at least a monthly basis. Conduct phenotypic analysis for any M^{pro} or M^{pro} cleavage site polymorphisms that are detected at a frequency ≥1% either globally or in the U.S. for any single month. These surveillance activities should continue for a period of 3 years post-approval, with re-assessment of the duration, frequency of reporting and additional protocol methods to occur on an annual basis.

The timetable you submitted on May 4, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2023
Interim Report Submission:	09/2023
Interim Report Submission:	12/2023
Interim Report Submission:	03/2024
Interim Report Submission:	06/2024
Interim Report Submission:	09/2024
Interim Report Submission:	12/2024
Interim Report Submission:	03/2025
Interim Report Submission:	06/2025
Interim Report Submission:	09/2025
Interim Report Submission:	12/2025
Interim Report Submission:	03/2026
Study Completion:	06/2026
Final Report Submission:	07/2026

In the quarterly interim reports, provide monthly counts of M^{pro} and M^{pro} cleavage site polymorphisms (minimum 0.1% frequency) globally, in the U.S., and in individual countries (any countries with a minimum of 1,000 sequences in at least one month). Provide ad-hoc reports (between quarterly reports) whenever a novel M^{pro} or M^{pro} cleavage site polymorphism is detected at a monthly frequency ≥1% either globally, in the U.S., or in an individual country with a minimum of 1,000 sequences.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of toxicity due to the potential

increase in the exposures of nirmatrelvir and/or metabolites in patients with severe renal impairment.

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

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).

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	04/2024
Final Report Submission:	07/2024

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.[4]

Submit clinical protocol(s) to your IND 153517 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

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 commitments:

4392-7 Submit the final study report with datasets for the ongoing trial, "An Interventional Efficacy And Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study To Investigate Nirmatrelvir/Ritonavir In Nonhospitalized Participants At Least 12 Years Of Age With Symptomatic COVID-19 Who Are Immunocompromised" (Study C4671034; NCT05438602).

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Interim (Topline Results) Submission:	09/2023
Trial Completion:	12/2023
Final Report Submission:	06/2024

4392-8 Submit the final study report with datasets for the ongoing trial, "A Phase 1, Open-Label Study To Evaluate The Pharmacokinetics, Safety, And Tolerability Of Orally Administered Nirmatrelvir/Ritonavir In Pregnant Women With Mild-To-Moderate COVID-19" (Study C4671035; NCT05386472).

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	07/2024
Final Report Submission:	12/2024

4392-9 Submit the final study report with datasets for the ongoing trial, "A Phase I, Multiple Dose, Open-Label Pharmacokinetic Study Of Nirmatrelvir/Ritonavir In Healthy Lactating Women" (Study C4671039; NCT05441215).

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	12/2023

Final Report Submission: 04/2024

4392-10 Conduct an observational study to evaluate pregnancy and infant outcomes following exposure to PAXLOVID during pregnancy.

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2023
Interim Report Submission:	03/2024
Interim Report Submission:	03/2025
Interim Report Submission:	03/2026
Interim Report Submission:	03/2027
Final Report Submission:	07/2028

4392-11 Submit the final study report with datasets for the ongoing trial, “An Interventional, Efficacy And Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study To Investigate A Repeat 5-Day Course Of Nirmatrelvir/Ritonavir Compared To Placebo/Ritonavir In Participants At Least 12 Years Of Age With Rebound Of COVID-19 Symptoms And Rapid Antigen Test Positivity” (Study C4671042; NCT05567952).

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	02/2024
Final Report Submission:	08/2024

4392-12 Conduct a study to evaluate the activity of nirmatrelvir (±ritonavir) in combination with remdesivir against SARS-CoV-2 in cell culture.

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	08/2023
Final Report Submission:	09/2023

4392-13 Conduct a study using cell culture assays to characterize the effect of nirmatrelvir/ritonavir on the anti-influenza virus activity of (a) oseltamivir and (b) baloxavir, and conversely the effect of (a) oseltamivir and (b) baloxavir on the anti-SARS-CoV-2 activity of nirmatrelvir/ritonavir.

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	09/2023
Final Report Submission:	10/2023

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4392-14 Complete the proposed ecotoxicity studies that are currently in progress and update the environmental analysis report.

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2023

4392-15 Submit three-month long-term and accelerated stability data for three batches of nirmatrelvir tablets manufactured at the (b) (4)

The timetable you submitted on May 1, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission:	07/2023

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 153517 for this product. 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/subjects 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. 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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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 Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at (301) 796-0807 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

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

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/

JOHN J FARLEY
05/25/2023 05:10:49 AM