Promoting the Quality of Medicines Plus (PQM+)

Scientific and technical information package for COVID-19 antivirals prescribed to prevent serious disease and death in high-risk populations infected with COVID-19

Nirmatrelvir tablets co-packaged with Ritonavir tablet; Molnupiravir capsule

August 2023

Package 2C

USAID FROM THE AMERICAN PEOPLE

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This document is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID) Cooperative Agreement No. AID-7200AA19CA00025. The contents are the responsibility of U.S. Pharmacopeial Convention (USP) and do not necessarily reflect the views of USAID or the United States Government.

About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

Suggested Citation

PQM+. 2023. Scientific and Technical Information Package for COVID-19 Antivirals Prescribed to Prevent Serious Disease and Death in High-Risk Populations Infected with COVID-19: Nirmatrelvir Tablets Co-packaged with Ritonavir Tablets; Molnupiravir Capsules. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.

Contents

Acknowledgements

European Medicines Agency (EMA) authored documents are cited in their original form as published by EMA (either as a PDF or online publication).

U.S. Food and Drug Administration (FDA) authored documents are cited in their original form as published by U.S. FDA. Advisory committee briefing documents provided to the U.S. FDA by Pfizer and Merck Sharp & Dohme LLC are for public release and were published on the U.S. FDA website.

U.S. National Institutes of Health (NIH) documents were authored by the COVID-19 Treatment Guidelines Panel. Specifically, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2023. The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (https://www.covid19treatmentguidelines.nih.gov/).

World Health Organization (WHO)-authored documents are cited in their original form as published by WHO (either as a PDF or online publication). Individual titles, place of publication, and year are contained in each original document except the one listed below. All documents were issued under License: CC BY-NC-SA 3.0 IGO

PQM+ would like to thank our implementing partner programs, Meeting Targets and Maintaining Epidemic Control (EpiC) and Reaching Impact, Saturation, and Epidemic Control (RISE), for their collaboration and support throughout the test-to-treat (T2T) program. We would also like to thank our collaborators from the national medicines regulatory authorities (NMRA) in each of the Test to Treat countries:

Directorate General of Drug Administration, Bangladesh
Botswana Medicines Regulatory Authority
L'Autorité Ivoirienne de Régulation Pharmaceutique, Cote d'Ivoire
Direccion Nacional de Medicamentos, El Salvador
Food and Drugs Authority Ghana
Ministry of Health, Lesotho
Pharmacy and Medicines Regulatory Authority, Malawi
Autoridade Nacional Reguladora de Medicamentos, Mozambique
Rwanda Food and Drugs Authority
Agence sénégalaise de Réglementation Pharmaceutique, Senegal

PQM+ would like to thank Carol Holtzman, Alison Collins, Elisabeth Ludeman, and Tobey Busch from USAID for their guidance. Thanks are also due to the PQM+ technical staff, Amanda Lewin, Diana Diaz Guzman, and Souly Phanouvong for the development of this document, and PQM+ editorial staff who provided valuable comments during the development of this document.

Acronyms

API	active pharmaceutical ingredients
EMA	European Medicines Agency
EUA	emergency use authorization
EUAL	emergency use assessment and listing
EUL	emergency use listing
FDA	U.S. Food and Drug Administration
NIH	U.S. National Institutes for Health
PHEIC	public health emergency of international concern
PQM+	Promoting the Quality of Medicines Plus
T2T	test-to-treat
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Package 2C. Tier C Document information (click each entry to link to document)

#	DOCUMENT TITLE	SOURCE
2C.1	EMA European Public Assessment Report – Medicine Overview (March 7, 2023)	EMA
2C.2	EMA European Public Assessment Report – Procedural Steps Taken and Scientific Information After Authorisation (June 27, 2023)	EMA
2C.3	EMA News: EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel	EMA
2C.4	U.S. FDA Paxlovid Approval Letter	U.S. FDA
2C.5	U.S. FDA News Release: FDA Approves First Oral Antiviral for Treatment of COVID-19 in Adults (May 25, 2023)	U.S. FDA
2C.6	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Administrative and Correspondence Documents	U.S. FDA
2C.7	U.S. FDA EUA Authorization letter – Paxlovid (May 25, 2023)	U.S. FDA
2C.8	U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19	U.S. FDA
2C.9	U.S. FDA Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers	Pfizer
2C.10	Pfizer Important Prescribing and Dispensing Information (April 5, 2022)	U.S. FDA
2C.11	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 23, 2022)	U.S. FDA
2C.12	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (March 18, 2022)	U.S. FDA

Package 2C. continued (click each entry to link to document)

2C.13	U.S. FDA Clinical Pharmacology EUA Summary Review (April 8, 2022)	U.S. FDA
2C.14	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (June 28, 2022)	U.S. FDA
2C.15	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (July 6, 2022)	U.S. FDA
2C.16	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (August 5, 2022)	U.S. FDA
2C.17	U.S. FDA Clinical Pharmacology EUA Summary Review (August 25, 2022)	U.S. FDA
2C.18	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (September 26, 2022)	U.S. FDA
2C.19	U.S. FDA Memorandum: Summary Basis for Revising Certain Conditions on Printed, Advertising and Promotional Materials (October 27, 2022)	U.S. FDA
2C.20	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)	U.S. FDA
2C.21	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (May 25, 2023)	U.S. FDA

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Document 2C.1

EMA European Public Assessment Report – Medicine Overview (March 7, 2023)

Document URL

https://www.ema.europa.eu/en/documents/overview/paxlovid-epar-medicine-overview_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid

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EMA/80728/2023
EMEA/H/C/005973

Paxlovid (*PF-07321332 / ritonavir*)

An overview of Paxlovid and why it is authorised in the EU

What is Paxlovid and what is it used for?

Paxlovid is a medicine used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

Paxlovid contains two active substances, PF-07321332 and ritonavir, in two different tablets.

How is Paxlovid used?

Paxlovid can only be obtained with a prescription. The recommended dose is two tablets, each containing 150 mg PF-07321332, plus one tablet containing 100 mg ritonavir, to be taken together by mouth twice a day for 5 days. Paxlovid should be given as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of the start of symptoms.

For more information about using Paxlovid, see the package leaflet or contact your doctor or pharmacist.

How does Paxlovid work?

Paxlovid is an antiviral medicine that reduces the ability of SARS-CoV-2 (the virus that causes COVID-19) to multiply in the body. The active substance PF-07321332 blocks the activity of an enzyme needed by the virus to multiply. Paxlovid also contains a low dose of the medicine ritonavir, which slows the breakdown of PF-07321332, enabling it to remain longer in the body at levels that affect the multiplication of the virus. Together, the active substances can help the body to overcome the virus infection, and prevent the disease becoming severe.

What benefits of Paxlovid have been shown in studies?

A main study involving patients with COVID-19 and at least one underlying condition putting them at risk of severe COVID-19 looked at the effects of Paxlovid on rate of hospitalisation or death within 28 days of treatment when compared with placebo (a dummy treatment). The analysis was done in patients who received Paxlovid within 5 days after COVID-19 symptoms began and who did not receive nor were expected to receive treatment with antibodies. Over the month following treatment, the rate of hospitalisation or death was 0.8% (8 out of 1,039) for patients who received Paxlovid, compared

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with 6.3% (66 out of 1,046) for those who received placebo. There were no deaths in the Paxlovid group and 12 deaths in the placebo group.

The majority of patients in the study were infected with the Delta variant. Based on laboratory studies, Paxlovid is also expected to be active against Omicron and other variants.

What are the risks associated with Paxlovid?

The most common side effects with Paxlovid (which may affect less than 1 in 10 people) are dysgeusia (taste disturbance), diarrhoea, headache and vomiting.

Paxlovid must not be used together with medicines that are harmful at high levels in the blood and whose breakdown in the body is reduced by ritonavir. Paxlovid must also not be taken by people who have just stopped these medicines as some of the medicine may still remain in the body. Paxlovid must also not be taken with medicines that may reduce its effectiveness or by patients who are taking St John's wort (a herbal preparation used to treat depression). To identify interactions with ritonavir, a drug interaction tool is available on the website of the company marketing Paxlovid which can be accessed through a QR code in the product information and outer carton.

For the full list of restrictions and side effects of Paxlovid, see the package leaflet.

Why is Paxlovid authorised in the EU?

Paxlovid was shown to be effective at reducing the risk of hospitalisation or death in patients with COVID-19 at increased risk of the disease becoming severe. The safety profile of Paxlovid was favourable and side effects were generally mild. However, the well-known effect of ritonavir on other medicines was a concern and advice is included in Paxlovid's product information. The European Medicines Agency concluded that Paxlovid's benefits are greater than its risks and it can be authorised for use in the EU.

Paxlovid was originally given 'conditional authorisation' because there was more evidence to come about the medicine. As the company has supplied the additional information necessary, the authorisation has been switched from conditional to full authorisation.

What measures are being taken to ensure the safe and effective use of Paxlovid?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Paxlovid have been included in the summary of product characteristics and the package leaflet, including a link to a drug interaction tool to identify interactions with ritonavir.

As for all medicines, data on the use of Paxlovid are continuously monitored. Suspected side effects reported with Paxlovid are carefully evaluated and any necessary action taken to protect patients.

Other information about Paxlovid

Paxlovid received a conditional marketing authorisation valid throughout the EU on 28 January 2022. This was switched to a full marketing authorisation on 24 February 2023.

Further information on Paxlovid can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/paxlovid

This overview was last updated in 02-2023.

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Document 2C.2

EMA European Public Assessment Report – Procedural Steps Taken and Scientific Information

Document URL

https://www.ema.europa.eu/en/documents/procedural-steps-after/paxlovid-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid

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Paxlovid

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0032	Update of section 4.4 of the SmPC in order to include a warning on the risk of hypertension and to recommend a monitoring of blood pressure, and update of section 4.8 to add 'hypertension' to the list of adverse drug reactions (ADRs) with frequency 'uncommon', based on review of aggregate post-	12/05/2023	23/06/2023	SmPC and PL	Hypertension was detected as a signal in post-marketing experience. Post marketing analysis revealed at a least possible causal relationship to Paxlovid, in terms of temporal association and lack of confounding factors. A warning was consequently added in section 4.4 of the SmPC to further alert prescribers on the risk of

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	marketing data. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				hypertension and to recommend the monitoring of blood pressure during Paxlovid therapy (self-monitoring for outpatients) in order to initiate or re-assess antihypertensive treatment if necessary. For more information, please refer to the Summary of Product Characteristics.
II/0037	Submission of the updated population modeling analysis report (PMAR-EQDD-C467a-Other-1463): population pharmacokinetics of nirmatrelvir/ritonavir after oral administration in adults with/without COVID-19 - a pooled analysis of phase 1/2/3 data. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/05/2023	n/a		
II/0036	Update of sections 4.4, and 4.5 of the SmPC in order to include a warning related to Immunosuppressants and to update the information regarding co-administration with Immunosuppressants following the assessment of procedure II/0010/G based on the cumulative review of the spontaneous reports of over-exposure/over-toxicity of immunosuppressants and literature review. In addition, the MAH took this opportunity to introduce minor editorial changes to the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2023	26/04/2023	SmPC	The Product Information has been updated to include a warning related to immunosuppressants, and to update the information regarding co-administration with immunosuppressants to enhance the physicians' attention on the complexity of the management in the target population. Such amendment follows the assessment of procedure II/0010/G based on the cumulative review of the spontaneous reports of over-exposure/over-toxicity of immunosuppressants and literature review. For more information, please refer to the Summary of Product Characteristics and Package Leaflet

IA/0041/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/04/2023	n/a		
IB/0038	B.II.d.2.z - Change in test procedure for the finished product - Other variation	07/03/2023	n/a		
II/0019/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.e - Change in the specification parameters	26/01/2023	24/02/2023	Annex II	The SmPC section 5.1 has been updated by deleting the text below: "This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary." The PL have been updated accordingly. The Annex II has been updated as follows: The three remaining specific obligations are deleted from

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	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.z - Change in control of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				the Annex II to the Opinion: 1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply. 2. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established. 3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided
II/0026/G	This was an application for a group of variations. - Update of section 4.6 to update information related to the nonclinical data on developmental toxicity without change the recommendation based on cases reported on on-going clinical trials C4671002, C4671005 and C4671006, or reported during post-marketing, and the pre- and post-natal development study report 21GR149. - Update of section 5.1 of the SmPC in order to include final clinical efficacy and safety data based on the pivotal C4671005 study. Section 5.1 of the SmPC is also updated to include the antiviral activity of nirmatrelvir, against the sub-variants B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.4, and BA.5,	26/01/2023	15/02/2023	SmPC and PL	This grouped variation application concerns the several updates of the SmPC generated from different data sources. In relation to pregnancy, data on animal studies showed there were no nirmatrelvir-related severe manifestations of developmental toxicity at the highest dose tested in rats and rabbits. There were no nirmatrelvir-related adverse effects on pre- and post-natal development up to the highest dose tested in rats. Clinical data included identified 7 cases of maternal exposure during pregnancy in the on-going clinical trials: in 4 of the 7 cases, female study participants received placebo, in 3 of the 7 cases the pregnancies occurred in female partners of male study participants receiving nirmatrelvir/ritonavir. There were no associated adverse events in any of the 3 cases. In all 3

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	antiretroviral resistance information based on in vitro assays and viral load rebound and treatment-emergent mutations observed in clinical practice. - Update of section 5.2 of the SmPC in order to update pharmacokinetic data on the effect of food on oral absorption following the submission of the results from studies C4671012, C4671013, C467104, C4671015 and C4671019. The first four studies are DDI studies conducted in healthy volunteers, with dabigatran, midazolam, carbamazepine and itraconazole, respectively. C4671019 was a phase 1, open-label, randomised, single dose, 2-sequence, 2-period crossover study to evaluate the effect of high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir following after single oral dose administration in healthy adult participants. The MAH has taken the opportunity to include editorial changes are included in sections 4.2, 4.5, 4.8 and 6.1 of the SmPC and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				cases the outcome of the pregnancies was unknown at the time of reporting. At the time of reporting there were 2 post-marketing cases of pregnancy. In 1 of the post-marketing cases, a female took nirmatrelvir/ritonavir at 27 weeks gestation and adverse events of Ageusia and Anosmia were co-reported. In the second post-marketing case no adverse were reported. Based on review of available pregnancy data, no update to the recommendation is considered necessary, although based on this review section 4.6 of the SmPC is slightly updated. In relation to pharmacodynamic properties, in vitro cell culture data showed nirmatrelvir antiviral activity against Omicron subvariants BA.1, BA.2, BA.4 and BA.5 with EC50 fold changes compared to wild-type of ≤1. Also, a list of SARS-CoV-2 Mpro amino acid substitutions selected by nirmatrelvir in cell culture (with EC50 fold change >5) have been included in the SmPC, although the clinical significance of these mutations needs to be further understood. Lastly, in relation to antiviral rebound, the SmPC was updated to indicate that post-treatment viral nasal RNA rebounds were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR, irrespective of COVID-19 symptoms. The incidence of viral rebound in EPIC-HR occurred in both the Paxlovid treated participants and the untreated (placebo) participants, but at higher incidence in the Paxlovid arm (6.96% vs. 4.08%). So far, viral rebounds and symptoms recurrences of COVID-19 are not associated with more severe disease or emergence of resistance. In relation to clinical efficacy, the first key secondary efficacy results from the pivotal trial C4671005 were

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					hospitalisation or death from any cause through Day 28 in the mITT1 analysis set who received treatment within 5 days of symptom onset was 66 of 1046 (6.310%) participants in the placebo group, and 9 of 1039 (0.866%) participants in the Paxlovid group, showing an 86.3% (72.6% to 93.1%) relative risk reduction in observed endpoint events. This change in the primary endpoint relative risk reduction from 87.8% as reported in the C4671005 primary completion date CSR was due to the reporting of a late event of a hospitalisation. This was a newly reported primary event (COVID-19-related hospitalization at Day 2) for a participant in the Paxlovid treatment group. For more information, please refer to the Summary of
II/0028/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters	02/02/2023	n/a		

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	and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IB/0033	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	24/01/2023	15/02/2023	SmPC, Labelling and PL	To update the product information to extend the shelf life of the finished product from '18 months' to '2 years' (section 6.3 of the SmPC) and to change the storage conditions from 'Do not store above 25 °C. Do not refrigerate or freeze.' to 'This medicinal product does not require any special storage conditions.'
PSUSA/10984 /202206	Periodic Safety Update EU Single assessment - (1r,2s,5s)-n-{(1s)-1-cyano-2-[(3s)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3- [3-methyl-n-(trifluoroacetyl)-l-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide / ritonavir (Paxlovid)	12/01/2023	n/a		PRAC Recommendation - maintenance

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IB/0035	B.I.d.z - Stability of AS - Other variation	11/01/2023	n/a		
II/0010/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC to add hypersensitivity to the list of adverse drug reactions with frequency uncommon and anaphylaxis with frequency rare, including a warning on hypersensitivity reactions, based on a cumulative search of the MAH safety database. The Package Leaflet is updated accordingly. Update of section 4.5 of the SmPC in order to add drug-drug interaction information with dabigatran and rivaroxaban (P-gp substrate) based on the clinical study results from study C4671012, a pharmacokinetic study to estimate the effect of Paxlovid on the pharmacokinetics of dabigatran; the Package Leaflet is updated accordingly. Update of section 4.5 of the SmPC in order to update the drug-drug interaction information of midazolam based on the clinical study results from study C4671013, a pharmacokinetic study to estimate the effect of Paxlovid on the pharmacokinetics of midazolam. The MAH has taken the opportunity to update sections 4.3, 4.4 and 4.5 of the SmPC in relation to the drug-drug interaction profile for Paxlovid: pethidine has been removed as a contraindicated medication; tadalafil, silodosin, eplenerone, ivabradine, voclosporin, eletriptan, tolvaptan, and apalutamide have been added as contraindicated	15/12/2022	22/12/2022	SmPC and PL	Based on a safety review on the use of Paxlovid, the following changes are included in the product information: • Anaphylaxis and other hypersensitivity reactions have been reported with Paxlovid. Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of Paxlovid. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care. • Concomitant administration of Paxlovid is expected to increase dabigatran concentrations resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran Summary of the product charactestics (SmPC) for further information. Rivaroxaban is not recommended as it's metabolisation may be impacted by the CYP3A4 inhibitory effect of Paxlovid but also its P-gp inhibitory effect. • The new information obtained from a drug-drug interaction study conducted with Paxlovid and midazolam does not downgrade the magnitude of interaction pertaining to inhibition of CYP3A4, although the pharmacokinetics information in the SmPC is updated accordingly. • Pethidine exposure is expected to decrease through the co-administration with Paxlovid due to the effect of ritonavir (as observed through the studies by Ramirez et al and Piscitelli et al). This indication will result in the increase of its metabolite known to be associated with opioid effects.

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	medications; and sirolimus and lercanidipine have been added to list of interactions in section 4.5 of the SmPC. Also drugs propoxyphene, bepridil, encainide, astemizole, norbuprenophine, vorapaxar and desipramine have been removed from the SmPC as they are no longer marketed into the EU. Lastly, the SmPC was also updated to incite for a multidisciplinary approach for best handling the potential co-medications. The MAH is taking the opportunity to include editorial updates in sections 4.3, 4.4, 4.5, 5.1 and 5.2 of the SmPC. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Therefore it is recommended to monitor for respiratory depression and sedation. • Sildenafil and tadalafil regardless of their intended used, i.e. to treat erectile dysfunction or pulmonary arterial hypertension, are contraindicated. • Ritonavir as a pharmacokinetic enhancer inhibits CYP3A4 is expected to increase the plasma concentrations of immunosuppressants such as cyclosporine, everolimus, sirolimus and tacrolimus. This co-administration should only be considered with close and regular monitoring of immunosuppressant serum concentrations, to reduce the dose of the immunosuppressant so that to avoid over exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed during the co-administration with Paxlovid but also after the treatment with Paxlovid. • Additional contraindicated medication were added as a conservative approach: silodosin, eplenerone, ivabradine, voclosporin, eletriptan, tolvaptan, and apalutamide. • Propoxyphene, bepridil, encainide, astemizole, norbuprenophine, vorapaxar and desipramine have been removed from Paxlovid SmPC, as they are no longer approved drugs. • Lercanidipine should be avoided in co-administration with Paxlovid. The differential recommendation as compared to other calcium channel inhibitors as lercanidipine is particularly sensitive to CYP3A4 inhibition. • Depending on the type of drug-drug interaction, a

IB/0034/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/12/2022	n/a		
IB/0029/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.z - Change in manufacture of the Finished Product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	01/12/2022	n/a		
R/0023	Renewal of the marketing authorisation.	10/11/2022	28/11/2022		

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IAIN/0031/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code A.3 - Administrative change - Change in name of the AS or of an excipient	22/11/2022	22/12/2022	SmPC, Annex II, Labelling and PL	
II/0017	Submission of the final report from study in vivo efficacy of Pf-07321332 as a single agent or in combination with ritonavir in Balb/C Mouse-Adapted SARS-CoV-2 Model. The objective of this study was to evaluate whether Ritonavir has in vivo antiviral activity against SARS-CoV-2 and whether combination of Ritonavir with PF-07321332 increased the exposure of PF-07321332 in the mouse model and further decreased viral lung replication. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/11/2022	n/a		
II/0016/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to include the adverse drug reactions: nausea with frequency common, abdominal pain with frequency uncommon and malaise with frequency rare; based on the global safety database of the MAH and literature review. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	13/10/2022	20/10/2022	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/09/2022	n/a		
IB/0022	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	19/09/2022	29/09/2022	SmPC	To change the summary of product characteristics, section 6.3 Shelf life from '1 year' to '18 months'.
IB/0020	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	15/09/2022	n/a		
II/0008	Submission of the final report from study PMAR-EQDD-C467a-DP4-1323, listed as a legally binding measure. This is the updated population pharmacokinetics module results including PK data from the patients enrolled in the EPIC-HR study of Paxlovid. C.I.13 - Other variations not specifically covered	15/09/2022	n/a		

IB/0025	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	09/09/2022	n/a		
IB/0027	B.I.b.z - Change in control of the AS - Other variation	08/09/2022	n/a		
II/0015	Submission of an exploratory lipid analysis conducted retrospectively using the left-over safety and PK samples from the multiple ascending dose (PART-2) of study C4671001 (phase I randomised controlled trial) submitted as part of the initial marketing authorisation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2022	n/a		
IB/0018	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	30/08/2022	29/09/2022	Annex II	To delete specific obligtion 4 in Annex II.
IA/0024	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	12/08/2022	n/a		
IA/0021	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	13/07/2022	n/a		

II/0012/G	This was an application for a group of variations. C.I.13 (type II): Submission of the whole body autoradiographic study report in rats with PF-07321332 (alone). C.I.13 (type II): Update of section 5.3 of the SmPC to indicate that no adverse effects were observed during the pre-and postnatal development study based on final study report for the pre- and postnatal development (21GR149). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/07/2022	29/09/2022	SmPC	
II/0009	Update of sections 4.3 and 4.5 of the SmPC in order to remove piroxicam as a contraindicated medicinal product and to indicate that piroxicam exposure may be decreased due to interaction with Paxlovid, based on scientific literature. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2022	01/07/2022	SmPC and PL	

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IB/0006	B.II.e.z - Change in container closure system of the Finished Product - Other variation	14/06/2022	n/a		
IA/0014/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/05/2022	n/a		
IAIN/0013	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	18/05/2022	n/a		
IB/0005/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.z - Change in control of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	11/05/2022	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0003/G	This was an application for a group of variations. B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	22/04/2022	n/a		
II/0001/G	This was an application for a group of variations.	22/04/2022	01/07/2022	PL	The Annex II has been updated to include the name and address of the new manufacturer responsible for batch

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	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP -				

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	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0002	B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	17/03/2022	n/a		

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Document 2C.3

EMA News: EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel

Document URL

https://www.ema.europa.eu/en/news/ema-issues-advice-use-paxlovid-pf-07321332-ritonavir-treatment-covid-19-rolling-review-starts

Reference website URL

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions-any-scientific-matter-human-medicines#use-of-

License

Not applicable

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel

News 16/12/2021

EMA's human medicines committee (CHMP) has issued advice on the use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19. The medicine, which is not yet authorised in the EU, can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe disease. Paxlovid should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. The two active substances of the medicine, PF-07321332 and ritonavir, which are available as separate tablets, should be taken together twice a day for 5 days.

EMA issued this advice to support national authorities who may decide on possible early use of the medicine prior to marketing authorisation, for example in emergency use settings, in the light of rising rates of infection and deaths due to COVID-19 across the EU.

The advice is based on interim results from the main study in non-hospitalised, unvaccinated patients who had symptomatic disease and at least one underlying condition putting them at risk of severe COVID-19. These data showed that Paxlovid reduced the risk of hospitalisation and death when treatment started within 5 days of the start of symptoms. About 1% of patients (6 out of 607) who took Paxlovid within five days of the start of symptoms were hospitalised within 28 days of starting treatment compared with 6.7% of patients (41 out of 612) given placebo (a dummy treatment); none of the patients in the Paxlovid group died compared with 10 patients in the placebo group.

In terms of safety, the most common side effects reported during treatment and up to 34 days after the last dose of Paxlovid were dysgeusia (taste disturbance), diarrhoea and vomiting.

Paxlovid must not be used with certain other medicines, either because due to its action it may lead to harmful increases in their blood levels, or because conversely some medicines may reduce the activity of Paxlovid itself. The list of medicines that must not be used with Paxlovid is

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included in the proposed conditions for use. Paxlovid must also not be used in patients with severely reduced kidney or liver function.

Paxlovid is not recommended during pregnancy and in people who can become pregnant and who are not using contraception. Breastfeeding should be interrupted during treatment. These recommendations are because laboratory studies in animals suggest that high doses of Paxlovid may impact the growth of the foetus.

EMA's proposed conditions of use will be published shortly on the EMA website.

The Agency's advice can now be used to support national recommendations on the possible use of the medicine before marketing authorisation.

Start of rolling review

In parallel to the provision of this advice, a more comprehensive rolling review started on 13 December 2021 ahead of a possible application for a marketing authorisation.

EMA will evaluate more complete data on the quality, safety and effectiveness of the medicine as they become available. The rolling review will continue until enough evidence is available for the company to submit a formal marketing authorisation application.

EMA will communicate further when a marketing authorisation application for the medicine has been submitted.

How the medicine is expected to work

Paxlovid is an oral antiviral medicine that reduces the ability of SARS-CoV-2 (the virus that causes COVID-19) to multiply in the body. The active substance PF-07321332 blocks the activity of an enzyme needed by the virus to multiply. Paxlovid also supplies a low dose of ritonavir (a protease inhibitor), which slows the breakdown of PF-07321332, enabling it to remain longer in the body at levels that affect the virus. Paxlovid is expected to reduce the need for hospitalisation in patients with COVID-19.

Related content

- Article 5(3) opinions: advice on the use of Paxlovid (PF-07321332 and ritonavir)
-
-
-
- COVID-19: latest updates (archive)
- Committee for Medicinal Products for Human Use (CHMP)

Contact point

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How to find us

Postal address and deliveries

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Document 2C.4

U.S. FDA Paxlovid Approval Letter

Document URL

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217188Orig1s000ltr.pdf

Reference website URL

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217188

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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

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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.

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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

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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.

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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

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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.

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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.

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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

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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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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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.

/s/

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

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Document 2C.5

U.S. FDA News Release: FDA Approves First Oral Antiviral for Treatment of COVID-19 in Adults (May 25, 2023)

Document URL

https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-antiviral-treatment-covid-19-adults

License

Not applicable

FDA NEWS RELEASE

FDA Approves First Oral Antiviral for Treatment of COVID-19 in Adults

For Immediate Release:

May 25, 2023

Español (https://www.fda.gov//news-events/press-announcements/la-fda-aprueba-el-primer-antiviral-de-ingestion-oral-para-el-tratamiento-del-covid-19-en-adultos)

Today, the U.S. Food and Drug Administration approved the oral antiviral Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid is the fourth drug—and first oral antiviral pill—approved by the FDA to treat COVID-19 in adults.

Paxlovid manufactured and packaged under the emergency use authorization (EUA) and distributed by the U.S. Department of Health and Human Services (https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Paxlovid/Pages/default.aspx)will continue to be available to ensure continued access for adults, as well as treatment of eligible children ages 12-18 who are not covered by today's approval. Paxlovid is not approved or authorized for use as a pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

"While the pandemic has been challenging for all of us, we have made great progress mitigating the impact of COVID-19 on our lives," said Patrizia Cavazzoni, M.D., director for the FDA's Center for Drug Evaluation and Research. "Today's approval demonstrates that Paxlovid has met the agency's rigorous standards for safety and effectiveness, and that it remains an important treatment option for people at high risk for progression to severe COVID-19, including those with prior immunity. The FDA remains committed to working with sponsors to facilitate the development of new prevention and treatment options for COVID-19."

Under the Federal Food, Drug, and Cosmetic Act, approval of a new drug requires, among other things, substantial evidence of effectiveness and a demonstration of safety for the drug's intended use(s). In considering approval of a drug, the FDA conducts a benefit-risk assessment based on rigorous scientific standards to ensure that the product's benefits outweigh its risks for the intended population.

The efficacy of Paxlovid was primarily supported by the final results of the EPIC-HR clinical trial. EPIC-HR was a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause through 28 days of follow-up by 86% compared to placebo among patients treated within five days of symptom onset and who did not receive COVID-19 therapeutic monoclonal antibody treatment. In this analysis, 977 patients received Paxlovid, and 989 patients received placebo, and among these patients, 0.9% who received Paxlovid were hospitalized due to COVID-19 or died from any cause during 28 days of follow-up compared to 6.5% of the patients who received the placebo.

Benefit of Paxlovid was observed in patients with prior immunity to the virus that causes COVID-19. Among patients in EPIC-HR who were antibody positive at trial enrollment, the risk of COVID-19-related hospitalization or death from any cause during 28 days of follow-up was 0.2% among the 490 patients treated with Paxlovid compared with 1.7% of the 479 patients receiving placebo. EPIC-SR was another clinical trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19. Although not statistically significant, among these vaccinated patients, there was a reduction in the risk of COVID-19 related hospitalization or death from any cause.

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EPIC-HR and EPIC-SR were randomized controlled trials and provide information about COVID-19 rebound. Data from these two trials showed that rebound in SARS-CoV-2 (RNA or virus) shedding or COVID-19 symptoms occurred in a subset of patients and happened in both the patients receiving Paxlovid and the placebo. Based on the data currently available to the FDA, there is not a clear association between Paxlovid treatment and COVID-19 rebound.

Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf) and authorized Fact Sheet for Health Care Providers (https://www.fda.gov/media/155050/download) for the Paxlovid EUA come with a boxed warning with instructions for prescribers. Prescribers should review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring. Prescribers should consider the benefit of Paxlovid treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.

In conjunction with today's approval, the FDA is providing all prescribers with important information for prescribing Paxlovid properly and safely, such as dosing instructions, potential side effects and information regarding drugs that may cause drug-drug interactions with Paxlovid. The most common side effects of taking Paxlovid include impaired sense of taste and diarrhea. Patients should discuss with their health care provider whether Paxlovid is right for them.

Related Information

- Coronavirus Disease (COVID-19) (https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19)

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The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Inquiries

Media:

FDA Office of Media Affairs

(mailto:FDAOMA@fda.hhs.gov)301-796-4540

Consumer:

888-INFO-FDA

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Document 2C.6

U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Administrative and Correspondence Documents

Document URL

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000AdminCorres.pdf

Reference website URL

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217188Orig1s000TOC.cfm

License

Not applicable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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IND 153517

MEETING MINUTES

Pfizer, Inc.
Attention: Karen Baker
Senior Director, Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Baker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Paxlovid (nirmatrelvir and ritonavir).

We also refer to the telecon between representatives of your firm and the FDA on May 24, 2022. The purpose of the meeting was to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 000105 to NDA 217188 and FDA feedback on CMC specific questions in preparation for NDA submission in June 2022.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Erica Keafer, Regulatory Business Process Manager at erica.keafer@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

David Claffey, Ph.D.
Branch Chief
Division of New Drug Products I
Office of New Drug Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: May 24, 2022, 12:00 PM – 1:00 PM

Meeting Location: Teleconference

Application Number: IND 153517

Product Name: Paxlovid (nirmatrelvir tablets and ritonavir tablets)

Indication: Treatment of patients with COVID-19 infection

Sponsor Name: Pfizer, Inc.

Regulatory Pathway: 505(b)(1)

Meeting Chair: David Claffey, Ph.D.

Meeting Recorder: Erica Keafer, M.S.

FDA ATTENDEES

Office of Pharmaceutical Quality (OPQ)

David Claffey, Ph.D.	Branch Chief, Division of New Drug Products 1 (DNDP I), Office of New Drug Products (ONDP)
Peter Guerrieri, Ph.D.	Senior Pharmaceutical Quality Assessor, DNDP I, ONDP
Shalini Anand, Ph.D.	Chemist, DNDP I, ONDP
Paresma Patel, Ph.D.	Branch Chief, Division of New Drugs API (DNDAPI) ONDP
Katherine Windsor, Ph.D.	Senior Pharmaceutical Quality Assessor, DNDAPI ONDP

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Derek Smith, Ph.D.	Deputy Director, Office of Pharmaceutical Manufacturing (OPMA)
Hang Guo, Ph.D.	Senior Pharmaceutical Quality Assessor, Division of Pharmaceutical Manufacturing Assessment I (DPMAI) Office of Pharmaceutical Manufacturing (OPMA),
Abdollah Koolivand, Ph.D.	Visiting Associate, DPMAI, OPMA
Elsbeth Chikhale, Ph.D.	Senior Pharmaceutical Quality Assessor, Division of Biopharmaceutics (DB), ONDP
Gerlie Gieser, Ph.D.	Pharmacologist, DB, ONDP
David Lewis, Ph.D.	Branch Chief, Division of Post-Marketing Activities I (DPMAI), Office of Lifecycle Drug Products (OLDP)
Ramesh Gopalaswamy, Ph.D.	Chemist, DPMAI, OLDP
Erica Keafer, M.S.	Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)

Office of Compliance

Commander, Tara Gooen Bizjak	Director of Policy Staff, Office of Manufacturing Quality (OMQ)
Diane Bruce, PharmD, RAC	Senior Advisor to OMQ-Drug Shortages, OMQ

Office of New Drugs

Sarah Connelly, M.D.	Clinical Team Leader, Division of Antivirals (DAV), Office of Infectious Diseases (OID)
Stephanie Troy, M.D.	Clinical Reviewer, DAV, OID
Alicia Moruf, PharmD, MPH	Senior Health Regulatory Project Manager, Office of Regulatory Operations (ORO)

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SPONSOR ATTENDEES

Lisa Skeens	Vice President, Global Regulatory Affairs Hospital Category
Karen Baker	Senior Director, Global Regulatory Affairs
William Dodge	Director, Regulatory CMC
Kara Follmann	Executive Director, Regulatory CMC
Beth Herman	Senior Manager, Regulatory CMC
Jared Piper	Director of Process Chemistry, Chemical R&D
Mike Coutant	Director, Analytical R&D
Daniel Arenson	Research Fellow, Pharmaceutical Sciences Team Lead
Olivier Dirat	Senior Director, CMC Advisory Office
Rodney (Matt) Weekly	Associate Research Fellow, Chemical Research and Development
Julia Wood	Senior Principal Scientist, Analytical R&D
Hugh Clarke	Senior Principal Scientist, Analytical R&D
Kimber Barnett	Research Fellow, Analytical R&D
Keith Masse	Senior Principal Scientist, Analytical R&D
Kazuko Sagawa	Research Fellow, Formulation Development
Patrick Daugherty	Senior Principle Scientist, Drug Product Design
Weili Yu	Associate Research Fellow, Drug Product Design
Timothy Graul	Director, Global CMC
Albert Pichieri	Director, Portfolio Lead – Drug Product, Launch Excellence, PGS
Glenn Schneider	Senior Director, PGS Design & Orchestration

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Declan O'Shea	Operations Lead, External Supply API
Frances Barry	QA Compliance Lead, Pfizer Ringaskiddy
Ashley Collins	Director, Portfolio Lead – Packaging, Launch Excellence, PGS
Paul Meenan	Associate Research Fellow, Drug Product Design
Michael Neidig	Director, Quality Systems
Bharat Damle	Executive Director, Clinical Pharmacology
Donna Cox	Clinical Pharmacology Group Lead

1.0 BACKGROUND

On December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3). Paxlovid consists of nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, is an HIV-1 protease inhibitor and CYP3A inhibitor.

With this meeting request, Pfizer is seeking to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 000105 to NDA 217188 and FDA feedback on CMC specific questions in preparation for NDA submission in June 2022.

FDA sent Preliminary Comments to Pfizer, Inc. on May 20, 2022.

2.0 DISCUSSION

The sponsor's questions are reproduced below. FDA's preliminary response to the questions, the sponsor's response to FDA's preliminary response, and the meeting discussion follow each question.

Question 1:
Pfizer will be including sites authorized in EUA 000105 in the initial NDA for PAXLOVID targeted for submission end of June 2022. For supply continuity, Pfizer will continue to add additional sites to the EUA following submission of the NDA and during the anticipated NDA review time period. A visual filing plan illustrating the upcoming site additions to the EUA or EUA/NDA is provided below.

Pfizer requests FDA concurrence with the strategy to align the CMC content in the EUA and NDA as needed and as soon as possible after the approval of the NDA.

Does FDA agree?

FDA Response to Question 1:

We encourage you to submit all changes that will impact commercial supply to the NDA – including additional drug substance and drug product manufacturing sites. You may choose to cross-reference the NDA in the EUA to align CMC content, as appropriate. If you choose to submit any changes concurrently to the EUA during the NDA review cycle, clearly outline any differences between the EUA and NDA submissions, along with justification for the differences.

This would appear to be a less regulatorily burdensome route and will aid in having more consistent product quality. However, if this is not possible, we would like to understand the rationale for your proposed approach – particularly for the proposed addition of the three sites in July 2022.

Further, we acknowledge the drug substance manufacturing sites you plan to add in Q4 2022: (b) (4) As you begin to obtain the CMC information (e.g., batch data) to support addition of these new sites, we encourage you to continue discussions with the Agency regarding the most suitable mechanism for each site addition. To help inform these discussions, we encourage you to communicate the following as you become aware: (1) more detailed estimated timelines for availability of the data to support each site (e.g., release data for the first three registration batches), and (2) any changes to the anticipated production schedule.

Additional recommendations:

For each drug substance manufacturing facility, the NDA should contain the following information:

- Release data for three batches of API manufactured to at least 10% of production scale and one drug product batch manufactured with API produced at the additional manufacturing site. The impurity profile and physical properties

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(e.g., polymorphic form) of the API should be comparable to that of API produced at the current proposed manufacturer(s).

- Detailed description of any changes to the manufacturing process or equipment differences used at the new API manufacturer relative to that described in the NDA for nirmatrelvir API production. Also, confirm that there are no changes to specifications for starting materials and intermediates used to manufacture API at the alternate manufacturing site.

- Any available stability data for API manufactured at the newly proposed site. We recommend that stability studies be initiated on three batches of API (manufactured to at least 10% of production scale) produced at each additional manufacturing site.

For each drug product manufacturing facility, the NDA should contain the following information:

- Release data of three drug product batches manufactured to at least 10% of the production scale

- Side by side comparison of the manufacturing process, equipment, batch size excipients specifications, information about container closure system to manufacture (or package) drug product proposed for alternate site/area. Please note that any minor changes should be delineated, and a justification should be provided to support the change, in the NDA.

- Updated 3.2.P.3.4 section which should include the control of critical steps and intermediates, along with summary tables for comparison of in-process data among different drug product batches.

- Batch manufacturing and packaging records along with yield/reconciliation summary tables for three drug product batches manufactured to at least 10% of the production scale.

- Any available stability data for drug product manufactured at the newly proposed site. We recommend that stability studies should be initiated on three batches of the drug product produced at each additional manufacturing site.

We also request that in support of the addition of each proposed new drug substance or drug product manufacturing site, that you provide evidence of comparable in vitro dissolution profile data of the post-change and pre-change drug products in various pH media and using the proposed NDA dissolution method. We recommend including in the comparison the in vitro dissolution profile data of a pivotal clinical trial (or other clinical study) lot as (one of) the reference/pre-change drug product lot(s).

We also recommend that you include all manufacturing and testing sites related to both the drug substance and drug product in the initial NDA submission in 356h form as this would allow for a timely review of each facility to ensure that materials manufactured and tested at each site conforms to quality standards expected of GMP facilities.

Sponsor's response to FDA preliminary comments, Question 1:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 1:

The sponsor indicated that at time of NDA submission, CMC data would not be available to support (b) (4) ritonavir tablet, (b) (4) nirmatrelvir tablet manufacturing site or the (b) (4) nirmatrelvir tablet testing site. However, data would be ready within one month of NDA submission – in July 2022. (b) (4) FDA stated that it would be acceptable to submit the information as amendments to the NDA within 30 days of NDA submission – and to reference this information in the NDA if amending the EUA. The sponsor agreed that they would take this approach. Regarding the submission of the three additional nirmatrelvir drug substance manufacturing sites, the sponsor stated that they would follow the FDA recommendation to communicate at a later time when more information is available about the proposals and their timelines. The sponsor thanked the FDA for their flexibility regarding this matter.

The sponsor wanted to clarify if manufacture of one batch of drug product was necessary to support new drug substance manufacturing sites for the NDA. The sponsor noted that submission of drug product data has not been a requirement for the EUA submission. The FDA clarified that the regulatory standards between an EUA and NDA are different.

FDA generally considers the principles of the Postapproval Changes to Drug Substances Guidance for Industry when considering addition of new drug substance sources for an NDA. FDA confirmed that at least one batch of drug product (manufactured with drug substance from a new site) should be submitted to support comparability of drug substance and addition of a new drug substance manufacture site. The sponsor asked the FDA if it would be possible to meet this requirement by submitting drug product batch information as an amendment during NDA review or as a post approval commitment. FDA agreed with submission of the supportive drug product batch data to support new drug substance manufacture sites as amendments during NDA review. FDA also confirmed that if the data would not be available during NDA review, that we may consider post-approval commitments based on the timelines for drug product manufacture. The sponsor asked for

confirmation that only one batch of drug product (manufactured at one drug product site) needed to be submitted to support any additional drug substance site, and FDA confirmed that would be sufficient. The sponsor thanked the FDA for their feedback and no further discussion occurred.

Question 2:

(b) (4)

FDA endorsed methods and specifications may vary between the EUA and NDA. EUA and/or NDA lots will be released in accordance with the respective methods and specifications approved at the time of testing.

Does FDA agree?

FDA Response to Question 2:

As noted in our response to Question 1, we encourage you to submit all changes that will impact commercial supply to the NDA. You may choose to cross-reference the NDA in the EUA to align CMC content, as appropriate.

If you choose to submit any changes concurrently to the EUA during the NDA review cycle, clearly outline any differences between the EUA and NDA submissions, along with justification for the differences as appropriate.

FDA is unable to comment (b) (4) FDA will continue to work with you to ensure continued supply of your product at the time of NDA approval.

Sponsor's response to FDA preliminary comments, Question 2:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 2:

(b) (4)

and acknowledged the FDAs feedback of not being able to comment at this time. The sponsor asked the FDA if they had any further feedback for Question 2. The FDA stated they had nothing additional to add and stated they will work closely with the sponsor during the NDA review period to ensure that the supply of the drug product is not interrupted. The sponsor thanked the FDA for their feedback and no further discussion occurred.

Question 3:

To meet projected demand, (b) (4)

via a Comparability Protocol to be included in the initial NDA.

Additional detail for each site in tabular format as requested in FDA's feedback in the pre-NDA Written Responses dated 13-Apr-2022 is provided in section 12.

(b) (4)

Does FDA agree?

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FDA Response to Question 3:

Refer to the Agency's response to Question 1 regarding information that should be provided to support any [redacted](b) (4)

The adequacy of the information provided to support [redacted](b) (4) – as well as any proposed comparability protocol – will be evaluated during NDA review.

All facilities involved in the disposition of a commercial drug product, including those used for storing commercial drug product under quarantine prior to a disposition decision should be included in the NDA. Refer to *"Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry".*

Sponsor's response to FDA preliminary comments, Question 3:
The Sponsor accepted FDA's response; no discussion occurred.

Discussion Question 3:
The Sponsor accepted FDA's response; no discussion occurred.

Question 4:
Does FDA agree with submission of the 3 month data for [redacted](b) (4) *during validation and that the totality of the data will allow for a* [redacted](b) (4) *retest period?*

FDA Response to Question 4:

Yes, your proposal to submit 3-month long-term and accelerated stability data for [redacted](b) (4) drug substance before mid-July appears acceptable.

The determination of the drug substance retest period will be made at the time of NDA review and will consider the totality of the data provided in the NDA, including supporting stability data for drug substance manufactured [redacted](b) (4). We encourage you to provide any updated drug substance stability data that may become available during the NDA review.

Sponsor's response to FDA preliminary comments, Question 4:
The Sponsor accepted FDA's response; no discussion occurred.

Discussion Question 4:
The Sponsor accepted FDA's response; no discussion occurred.

Question 5:

Does FDA agree with the submission of the 9 month data in June and the 12 month data in mid-September to support the 24 month shelf life?

FDA Response to Question 5:

Generally, we expect that at least 12 months of long-term stability data and 6 months of accelerated stability data for three primary drug product batches be included in the initial NDA submission per the recommendations in ICH Q1A(R2). However, *for a product being developed to address an unmet medical need, we are willing to accept less stability data for the primary batches in the initial NDA submission.* Therefore, your proposal to submit 9-month data at the time of NDA submission and 12-month data in mid-September appears acceptable.

The determination of the drug product expiry period will be made during NDA review and will be based upon the totality of the submitted data. Please submit all the available supporting data (e.g., developmental batches data) and additional data which may become available during NDA review.

Further, we request that you provide all available direct and supportive stability data and risk assessments for ritonavir tablets from each of the sources in the proposed blisters to support the proposed drug product expiry period.

Sponsor's response to FDA preliminary comments, Question 5:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 5:

The sponsor thanked the FDA for their feedback regarding their stability plans. The sponsor stated (b) (4) They also reiterated that they would submit drug product stability updates to the NDA in September 2022.

The FDA asked about the extent of available stability data for the ritonavir tablets from the proposed (b) (4) sources in the commercial blister packaging. The sponsor indicated that three months stability would be available for the AbbVie product and release data would be available for the Hetero product. The FDA acknowledged that drug product stability data were available for ritonavir tablets in other packaging configurations, but that the limited data in the proposed commercial blister packaging would require extensive justification. FDA encouraged the sponsor to include all available justification to support the ritonavir tablet expiry period. The sponsor confirmed their understanding and indicated that they have a modeling approach to justify shelf life together with stability data from AbbVie and Hetero. The

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FDA reiterated that they should provide all available data to justify the ritonavir tablet expiry period in the commercial blister packaging.

Question 6:

The Pfizer NDA will cross-reference the suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product supported by Letters of Authorization as was done in the EUA. To ensure projected supply, multiple suppliers for Ritonavir bulk tablets will be needed in the NDA, similar to the EUA. Current plans include AbbVie Inc (NDA 022417), Hetero Labs LTD Unit III (ANDA 204587) (b) (4)

Does FDA agree with the approach?

FDA Response to Question 6:

Your proposal to cross-reference the suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product, supported by Letters of Authorization, appears reasonable. We recommend that you include all facilities (testing and manufacturing) involved with suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product and the corresponding DMFs (as applicable) in the NDA.

As you propose to include multiple suppliers of ritonavir tablets (b) (4) in the finished drug product is critical for its performance, we recommend that you include a control (b) (4) in the release and stability specifications for ritonavir tablets.

Sponsor's response to FDA preliminary comments, Question 6:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 6:

The sponsor stated the NDA will cross reference the suppliers for ANDA ritonavir sources and acknowledges the FDA agrees with this approach. The sponsor requested clarification on the need for polymorphic form testing based on AbbVie and Hetero data indicating no change (b) (4) over time. The sponsor proposed to include the rationale as to why testing was not needed. The FDA recommended that the sponsor test batches at release and on stability, as this is a critical quality attribute known to impact bioavailability, and use of (b) (4) different ritonavir tablets from different suppliers/processes is proposed. These testing data

may be used to justify reduction of this testing at a future date. The sponsor stated they would discuss this matter internally and no other discussion occurred.

ADDITIONAL COMMENTS

1. We remind you to address all recommendations in the 16-DEC-2021 comments from the Agency provided under EUA 105 outlining updated nirmatrelvir drug substance information to be provided in any future NDA submission. For example, provide details of your control strategy for particle size distribution, including justification (e.g., results from your bioavailability studies) for any proposed particle size controls.

2. Regarding your 21-DEC-2021 Response to Comment #11 on environmental impacts, please include a similar analysis under the NDA (b) (4) [redacted]

3. In the NDA submission, provide sufficient justification for any proposed exclusion of tests that were included in the nirmatrelvir drug substance specification at the time of emergency use authorization of PAXLOVID.

Sponsor's response to FDA preliminary comments, Additional Comments 1 - 3:

The Sponsor accepted FDA's response; no discussion occurred.

ADDITIONAL COMMENTS

4. FDA understands that for the NDA you plan to (b) (4) [redacted] The acceptability of these proposals will be determined during NDA review when the supporting data/information become available for FDA evaluation.

(b) (4) [redacted]

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(b) (4)

Sponsor's response to FDA preliminary comments, Additional Comment 4:

Pfizer confirmed they would provide an update for Additional Comment 4 at the May 24, 2022, meeting.

Discussion, Additional Comment 4:

(b) (4)

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Other Discussion: The sponsor asked about OPQ/sponsor communication during the NDA review. The FDA indicated that given the complexity and unusual interrelated nature of the NDA/EUA issues, that OPQ is open to scheduling regular (e.g., monthly) meetings with the sponsor during NDA review to discuss CMC issues.

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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.

/s/

DAVID J CLAFFEY
05/26/2022 03:10:55 PM

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IND 153517

MEETING REQUEST-
WRITTEN RESPONSES

Pfizer Inc.
Attention: Karen Baker
Senior Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Baker:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act Paxlovid (nirmatrelvir and ritonavir).

We also refer to your submission dated February 15, 2022, containing a meeting request. The purpose of the requested meeting was to obtain the Agency's advice regarding your planned new drug application (NDA) for the use of this drug in the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death.

Further reference is made to our Meeting Granted letter dated March 2, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 15, 2022, background package.

[1]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.

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If you have any questions, call me, at (301) 960-9339 or the Division's mainline at, (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Talia Lindheimer
Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Written Responses
- Bioanalytical Method Performance Template
- Clinical Pharmacology In Vitro and In Vivo Study Table Template

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FDA U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: 153517

Product Name: Paxlovid (nirmatrelvir and ritonavir)

Indication: Treatment of adult COVID-19 patients (b) (4) [redacted]

Sponsor Name: Pfizer, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

An Emergency Use Authorization (EUA) for the use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death was initially authorized on December 22, 2021, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3). Paxlovid consists of nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, is an HIV-1 protease inhibitor and CYP3A inhibitor.

Pfizer is pursuing a marketing application for Paxlovid for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) [redacted] who are at high risk for progression to severe COVID-19, including hospitalization or death.

With this meeting request, Pfizer is seeking the Agency's feedback on the structure, format, and data plan for their future NDA submission including:

1. Sufficiency of nonclinical toxicology safety studies,

2. Nonclinical antiviral resistance assessments,

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3. Planned integration of safety data (Studies 1005 (EPIC-HR) and 1002 (EPIC-SR)) from PAXLOVID clinical trials and proposed format, standards, and structure of the datasets to be submitted,

4. Viral sequencing reports, and

5. Format and criteria of safety narratives.

2.0 QUESTIONS AND RESPONSES

General FDA Comments:

After a complete review of your Pre-NDA meeting request and briefing document, and as described in both the cover letter as well as in the Executive Summary of the briefing document, the information implies you plan to submit a new drug application (NDA) by the end of June 2022 for the following indication:

- the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.

We also note in section **4.2 Proposed Indication** of your background package you state,

Supportive studies to be included in the nirmatrelvir/ritonavir dossier are 2 ongoing pivotal clinical Studies (1002 [EPIC-SR], 1006 [EPIC-PEP]) (b) (4) *at the time of submission of the NDA. These pivotal trials will support licensure for the following indications:*

- *For the treatment of adult patients* (b) (4) *who are at* (b) (4) *risk of progressing to severe disease (Study 1002).*

(b) (4)

It is not clear if you plan to include the following indications in your planned original NDA submission:

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1. For individuals at [redacted] risk for progression to severe COVID-19, [redacted]

Please clarify the indication/claims that will be submitted at the time of your original NDA submission. Please note that a major amendment to an unapproved NDA may not include data to support an indication or claim that was not included in the original NDA submission, but it may include data to support a minor modification of the indication or claim that was included in the original NDA submission (21 CFR 314.60(b)(6)).

Please refer to the below comments regarding recommended content to be included with the original NDA.

2.1. Non-Clinical

Question 1: Does the Agency agree that the nonclinical safety studies undertaken, as outlined below, are sufficient to support NDA 217188? All components of the nonclinical safety package have been submitted to the IND with exception of the ongoing PPND study in rats. The sponsor intends to submit the PPND study report in April 2022. Upon completion and submission of the PPND study, the sponsor considers the nonclinical safety package complete for the NDA submission of PAXLOVID.

FDA Response to Question 1: Yes, we agree that nonclinical safety studies undertaken are sufficient to support NDA 217188. We also remind you that, besides the final report of the ongoing pre- and postnatal development (PPND) study in rats, you have only submitted unaudited draft reports of the 1-month repeat-dose toxicity studies in rats (#21GR122) and monkeys (#21GR125) (on November 24, 2021, to support EUA 105). It's unclear whether you plan to include the final reports of the 1-month repeat-dose toxicity studies in the NDA submission. Please comment on when you plan to submit the final reports for these studies.

Question 2: Does the Agency agree that the nonclinical virology antiviral resistance studies undertaken or planned, as outlined below in Table 3, are sufficient to support NDA 217188? Upon completion of the studies, the sponsor considers the nonclinical virology antiviral resistance package complete for the NDA submission of PAXLOVID and will have data to update the relevant section of the label.

FDA Response to Question 2: We do not fully agree. While we agree that nonclinical resistance studies using SARS-CoV-2 are more likely to be relevant than those using MHV, and results will be interpreted accordingly, we still request the MHV selection study report PF-07321332_12Oct21_035634 be included in the NDA as this study could still be supportive for identifying potentially important nirmatrelvir resistance pathways. For example, nirmatrelvir selection of MHV resulted in the emergence of the Mpro S144A substitution (as well as other substitutions), which, when engineered into a recombinant SARS-CoV-2 Mpro enzyme, reduced nirmatrelvir susceptibility by 92-fold

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in a biochemical assay. The MHV selection study confirmed that this substitution could emerge during viral replication in the presence of nirmatrelvir selective pressure.

Please also continue to phenotypically characterize specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility. This includes analyses of recombinant viruses encoding the substitutions of interest as described under EUA Condition "O1" (letter March 17, 2022), as well as cell culture and/or biochemical phenotypic analyses of other potential nirmatrelvir resistance-associated substitutions identified in nonclinical and clinical studies (e.g., treatment-emergent substitutions identified in Study 1005). Include a current report with cumulative data from these studies in the NDA. In the report include a summary of phenotypic analyses that are ongoing and planned at the time of NDA submission.

Please also plan to include all other supporting nonclinical virology-related study reports (e.g., mechanism of action; biochemical and cell culture antiviral activity; combination antiviral activity with ritonavir, remdesivir or other antiviral agents; cytotoxicity).

Please evaluate in cell culture assays 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. Completion of these studies would not be required for the initial NDA, but we recommend the studies are at least ongoing at the time of NDA submission, so data are available in a timely manner to inform the potential use of these agents in individuals co-infected with SARS-CoV-2 and influenza virus.

Please include a summary of virology studies in NDA Module 2.

2.2. Clinical

Question 3: For the NDA, the sponsor is planning to pool available safety data from ongoing clinical studies for PAXLOVID and summarize in the SCS. The integrated safety data will include data from Study 1005 PCD CSR, and Study 1002. (b) (4) Safety data from Study 1006 (expected to be completed at the time of submission for the NDA), following 5 or 10-day dosing regimen of PAXLOVID, will be provided in the SCS and would not be pooled with Studies 1005 and 1002. Does the Agency agree with (b) (4) presentation of separate pediatric (Study 1026) and EPIC-PEP (Study 1006) safety data for evaluating the overall safety of PAXLOVID in COVID-19 patients? Also, does the Agency agree with the analyses outlined in the iSAP?

FDA Response to Question 3: As noted in our opening General FDA Comments, please clarify the proposed original NDA indication(s). You indicate in your background package (b) (4)

[redacted] Based on this understanding, we provide the below comments regarding Question 3:

1. Please provide timelines on the expected safety and efficacy data locks for EPIC-PEP and EPIC-SR and timelines for these trial clinical study reports.

2. We strongly recommend that the original NDA incorporates complete efficacy and safety results from EPIC-HR along with at least EPIC-PEP and preferably both EPIC-PEP and EPIC-SR. Our recommendation is based on the following:

   a. [redacted] As mentioned in the General FDA comments, any additional claims that are not included in the initial NDA would be reviewed under a new NDA review clock or as efficacy supplements; [redacted].

   b. As stated in the FDA Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), FDA will consider a number of factors when determining whether to rely on a single adequate and well-controlled clinical investigation to support an NDA. These factors may include the persuasiveness of the single trial, the robustness of the confirmatory evidence, the seriousness of the disease and whether there is an unmet medical need, the size of the patient population, and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

      While we acknowledge the robustness of the results for EPIC-HR, and the nonclinical supportive data, we believe additional data from EPIC-PEP and/or EPIC-SR trials could support effectiveness and provide broader information about the drug's effectiveness. Because EPIC-PEP should be complete and EPIC-SR should be within 3 months of completion at the time you currently plan to submit your NDA, we strongly encourage you to

include either or both of these Phase 2/3 trials with the submission of the original NDA.

c. We note that even under a rolling review, application sections are expected to be complete at the time of submission (e.g., we would expect submission of a complete clinical section at the time of submission). You will need to submit a request for rolling review if a rolling review is desired.

We would be willing to have an additional meeting to discuss the proposed contents of an original NDA that include EPIC-PEP efficacy data or EPIC-PEP and EPIC-SR efficacy data. Please review the FDA guidance, *"Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry"* (December 2017)[2], to ensure you submit the appropriate meeting request type. This will facilitate the Agency's alignment of resources to provide an efficient and timely response to your meeting request.

3. (b) (4)

4. While the pooling strategy for the safety data does not seem unreasonable, we do not agree with the quantity of data being proposed to support this NDA as outlined above and recommend inclusion of EPIC-PEP and/or EPIC-SR efficacy data with an original NDA submission.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry

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2.3. Clinical Virology

Question 4: Does the Agency agree that submission of in vitro infectivity/phenotypic data from Study 1005 breakthrough cases and the final viral sequencing report including raw sequencing data is sufficient to support NDA approval?

FDA Response to Question 4:
We do not fully agree. As noted above (Question 2: Antiviral Resistance Assessments), and in addition to your planned analyses of samples from "breakthrough" cases, please also continue to phenotypically characterize specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies. These analyses should include nirmatrelvir treatment-emergent substitutions identified in Study 1005 regardless of whether they were detected in samples from "breakthrough" cases. Include a current report with cumulative data from these studies in the NDA. In the report include a summary of phenotypic analyses that are ongoing and planned at the time of NDA submission.

2.4. Narrative Strategy

Question 5: The sponsor is planning to continue to write hybrid narratives for safety events using the same format as submitted in the PAXLOVID EUA and Study 1005 CSRs. The sponsor does not plan to provide completed CRFs for participants with safety narratives. Does the Agency agree with the proposed safety narrative strategy for NDA 217188?

FDA Response to Question 5: We request that you include safety narratives for subjects with Grade 3 or higher AEs, significant hypersensitivity reactions, and subjects who meet DILI criteria. Otherwise, the proposed safety narrative strategy appears reasonable.

2.5. Data Standards

Question 6: Does the Agency agree, as outlined below, with the proposed format, standards and structure of the datasets that are planned to be submitted with the NDA?

FDA Response to Question 6: Your overall proposed plan appears reasonable. In regard to the Clinical Virology datasets, we generally agree with your plans for the submission of viral sequencing data as previously conducted for Study 1005. More specifically, please include available, cumulative raw NGS fastq data files along with an associated cumulative amino acid frequency table following the same formats as previously done for Study 1005 for the EUA. In the frequency table, please include an additional column flagging all data rows that are updated or new relative to the latest table/dataset submitted to the EUA (i.e., latest EUA submission by the date of

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NDA submission). Note that if it helps to streamline the virology datasets included in the NDA, it is not necessary to assemble and submit the more comprehensive analysis ready datasets (e.g., ADVIRG and CMBVIRG).

2.6. Regulatory

Question 7: The sponsor is planning to submit a separate CMC specific briefing document ahead of the NDA submission. In the meantime, the sponsor would like to understand whether it is acceptable to discuss certain CMC questions related to the NDA preparation following the accelerated communication pathways agreed for the EUA. For example, if the sponsor requires clarification, seeks guidance, or likes to provide an update on the commitments made in the EUA that impact the NDA, eg, to revise the dissolution method, would the Agency agree to communication or meetings under the umbrella of the EUA to ensure alignment between the Agency and the sponsor?

FDA Response to Question 7: We encourage you to request a pre-NDA CMC-specific meeting. In order to facilitate your NDA submission, we will make every effort to address other requests for clarification, guidance or comments regarding dissolution related or other CMC information in a timely manner, as resources permit.

Question 8: In consideration that an Advisory Committee meeting was not convened prior to the issuance of the EUA 000105 for PAXLOVID, can the Agency confirm that an Advisory Committee meeting is not expected to be convened prior to approval of the NDA?

FDA Response to Question 8: The Agency's decision to hold an Advisory Committee meeting for a new molecular entity or new chemical entity will be made at the time FDA filing (i.e., 60 days after receipt of the original NDA).

Question 9: The sponsor submitted a request for Fast Track Designation for PAXLOVID to IND 153517 on 28 January 2022. Can the Agency confirm that relevant criteria are met such that PAXLOVID is also eligible for Priority Review?

FDA Response to Question 9: Qualifying criteria for priority review designation can be found within the FDA Guidance, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014)[3]. The Agency will determine at the time of NDA filing whether the proposed product would be a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Pfizer may submit a request for priority review with the original NDA submission if they believe they meet the qualifying criteria for Priority Review.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

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Question 10: The sponsor plans [redacted] (b) (4) [redacted]. The sponsor proposes to also submit the available data sets to the NDA for consideration. Does the agency agree that these data sets can be submitted to the NDA for review?

FDA Response to Question 10: As noted in our response to Question 3, we strongly recommend that you do not submit your NDA until you can incorporate, at a minimum, complete safety and efficacy results from at least EPIC-PEP. We also remind you that application sections are expected to be complete at the time of NDA submission [redacted] (b) (4) [redacted] Please refer to the General FDA Comments for additional information.

2.7. Additional Comments

1. To facilitate efficient review of your clinical pharmacology information, please submit the following summary documents with your NDA 1) the provided method validation template for each respective clinical pharmacology study and 2) the attached in vitro ADME and in vivo PK study table template as a MS Word document file (.doc or .docx). A pdf copy of the template for each summary document is included at the end of this Written Response.

2. Please plan to provide a comprehensive review of post-authorization safety events with PAXLOVID in your NDA submission, including reports of events that may have occurred as a result of drug-drug interactions. This review should also include an assessment of post-authorization events related to the warnings and precautions in Norvir labeling, such as hypersensitivity reactions and pancreatitis.

3. The design of the Paxlovid 150 mg;100 mg packaging configuration is not optimized [redacted] (b) (4) [redacted], despite labeling mitigations. To minimize confusion and potential sources of medication error, we recommend you explore and develop a more optimal packaging configuration for NDA submission [redacted] (b) (4) [redacted] and is consistent with dosing.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed in this document.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

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- At this time, a preliminary discussion was not held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 INCLUSION OF MINORITIES IN CLINICAL TRIALS

The Agency encourages the inclusion of a diverse population in all phases of drug development. This inclusion helps to ensure that medical products are safe and effective for everyone. We strongly encourage the enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities. Please incorporate strategies to ensure that a diverse population is included in your current and future COVID-19 clinical trials.

5.0 PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric*

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Study Plans and Amended Pediatric Study Plans.[4] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[5]

6.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

7.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start/end of trial period (i.e., method of assignment of study events to a specific study

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period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

8.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

9.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

[10] https://www.fda.gov/media/85061/download

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BioAnalytical method validation summary

Regarding NDA 217188, please complete the bioanalytical method performance summary table below for for each clinical pharmacology study. Do not delete any rows from the tables. Include any other additional bioanalytical information in a separate table that might be relevant for review in your NDA submission. We recommend you submit these tables in eCTD Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods as pdf and docx formats.

Table 1. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	Eg. Table 1 of report # 123
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 x to y% x to y%	Table y of 2 report #123
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 ≤ x% ≤ x%	Table 4 of report #123
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: Product A Product B and/or C	 x to y% x to y%	Table 5 of report #123
	Inter-batch %CV QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 6 of report #123
	Total Error (TE) QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 7 of report #123
Selectivity & matrix	Number of total lots tested. Range of observed bias. State any issue		

effect		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue	
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue	
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue	
Dilution linearity & hook effect	Highest concentration tested and number of dilution factors. Range of observed bias	
Bench-top/process stability	Describe summary data here Product A Product B/C	
Freeze-Thaw stability	Describe summary data here Product A Product B/C	
Long-term storage	Describe summary data here Product A Product B/C	
Parallelism	Describe summary data here.	
Carry over	Describe summary data here	
Method performance in study number (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	(including incurred sample reanalysis (ISR))	
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV	
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2 below.

Table 2. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink		
Changes in method		
New validated assay range if any		
Validation parameters	**Cross-validation performance**	**Source location (hyperlinked)**

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Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

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Clinical Pharmacology In Vitro and In Vivo Study Table Template

For the following clinical pharmacology study types, please provide the below requested information in MS Word format:

In Vitro ADME Studies

Report Title	
Study Type	
Positive control(s) and concentrations	
Negative control(s) and concentration	
Report Number (with hyperlink to the full report)	
Study System (for example whole blood, plasma, recombinant enzymes, transfected cells, cryopreserved hepatocytes etc.)	
Method	Note: Include a very brief description of the methods. For drug interaction studies, please use cutoff criteria recommended in FDA drug interaction guidance.
Results	Note: Include a brief description of the major findings of the study. Also include the results of the positive control when applicable.
Discussion/Conclusion	Provide a succinct discussion of the results and their clinical relevance. Please indicate if a follow up in vivo trial was conducted to confirm the in vitro findings. If yes, please include the hyperlink to the complete study report. If not, please indicate why a follow up in vivo trial was not conducted.

In Vivo PK Studies

Location	Study # with hyperlink
Title	
Brief Description of Trial Design	
PK sample collection times	
Results	For each analyte, please include a table with PK parameters (for example, AUC, Cmax, Ctrough (if applicable), t1/2). For each comparison of PK parameters between groups, include a table of statistical comparisons (if applicable) of the PK parameters, including (GLSMs, GLSM ratio, 90% CI)

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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.

/s/

SUZANNE K STRAYHORN
04/13/2022 09:35:03 AM

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Document 2C.7

U.S. FDA EUA Authorization letter – Paxlovid (May 25, 2023)

Document URL

https://www.fda.gov/media/155049/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

Not applicable

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May 25, 2023

Pfizer, Inc.
Attention: Karen Baker
Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

RE: Emergency Use Authorization 105

Dear Ms. Baker:

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 22, 2021, the FDA issued an EUA for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020; U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020). *See* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

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older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. At that time, PAXLOVID was not FDA-approved for any indication.

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease inhibitor (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease), co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication.

FDA subsequently reissued the Letter of Authorization (LOA) on March 17, 2022[3], April 14, 2022[4], July 6, 2022[5], August 5, 2022[6], October 27, 2022[7], and February 1, 2023.[8]

On May 25, 2023, FDA approved NDA 217188 for PAXLOVID, which is indicated for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

On May 25, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the February 1, 2023 letter in its entirety, to incorporate revisions to the authorized use for PAXLOVID under this EUA, to revise condition L on the monitoring and analysis of SARS-CoV-2 variants, and to remove certain post-authorization requirements from this LOA that are adequately addressed as post-market requirements or post-market commitments associated with the approval of NDA 217188.

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[3] In its March 17, 2022 revision, FDA revised the LOA to add a new condition of authorization regarding registration and listing. Condition H in the LOA was also revised to require Pfizer to recall distributed product, upon request by FDA, in the event a significant quality problem is identified that impacts already distributed PAXLOVID.

[4] In its April 14, 2022 revision, FDA revised the LOA to authorize an additional dose pack presentation of PAXLOVID with appropriate dosing for patients within the scope of this authorization with moderate renal impairment. Corresponding revisions were also incorporated into the "How Supplied" section of the Fact Sheet for Healthcare Providers.

[5] In its July 6, 2022 revision, FDA authorized state-licensed pharmacists to prescribe PAXLOVID subject to certain conditions detailed in Section II (Scope of Authorization) of this LOA. Corresponding revisions were also incorporated into the Fact Sheet for Healthcare Providers. Updates were also incorporated to certain post-authorization requirements detailed in Condition O of this letter.

[6] In its August 5, 2022 revision, FDA revised the LOA to add new post-authorization requirements in Condition O of this letter for Pfizer to conduct a clinical trial in patients with "COVID-19 rebound" and a clinical trial evaluating different durations of treatment in immunocompromised patients with mild-to-moderate COVID-19. The Fact Sheet for Patients, Parents, and Caregivers was also revised to include additional clarifying information on how to take PAXLOVID, which included pictures of packaging and tablets for both dosing presentations.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition X of this letter. Condition W was also revised to require that all printed matter, advertising and promotional materials relating to the use of PAXLOVID under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

[8] In its February 1, 2023 revision, FDA revised the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization required, in addition to other requirements, that adults and pediatric patients (12 years of age and older weighing at least 40 kg) have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes were also made to the authorized Fact Sheets. Condition O in this letter was also revised based on the completion of a post-authorization requirement. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include new information on drug-drug interactions.

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Corresponding revisions, when appropriate, were incorporated into the authorized Fact Sheets. The authorized Fact Sheet for Healthcare Providers was also revised to include a boxed warning on the identification of and assessment for drug-drug interactions with PAXLOVID. Relevant information on drug-drug interactions was also incorporated in the Fact Sheet for Patients, Parents and Caregivers.

Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of PAXLOVID for the treatment of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.[9,10]

[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[10] Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-

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II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)[11], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- PAXLOVID may only be used by healthcare providers for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death;

  Limitations on Authorized Use

  - PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[12]
  - PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
  - PAXLOVID is not authorized for use for longer than 5 consecutive days.

- PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.[13]

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moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days). Additionally, although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of the EUA, and PAXLOVID is not FDA-approved for individuals younger than 18 years of age. Apart from the previous sentence, all reference to the term "PAXLOVID" in this LOA refer to product that is labeled in accordance with this EUA. See "Product Description" in this LOA for more information.

[11] "Authorized Distributor(s)" are identified by Pfizer as an entity or entities allowed to distribute authorized PAXLOVID.

[12] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See Section 201(a)(1) of the Act.

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- PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

    - Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
    - Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

- The use of PAXLOVID covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

PAXLOVID consists of 150 mg tablets of nirmatrelvir that are co-packaged with 100 mg tablet ritonavir.

PAXLOVID is authorized to be distributed in the following presentations, which are distinguishable by the specific amount of active ingredient per treatment course:

- *300 mg nirmatrelvir;100 mg ritonavir*: Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."
- *150 mg nirmatrelvir; 100 mg ritonavir*[14]: Each carton contains 20 tablets divided in 5 daily-dose blister cards. Each blister card contains 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."

The authorized storage and handling information for PAXLOVID is included in the authorized Fact Sheet for Healthcare Providers.

PAXLOVID is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers,

[14] The 150 mg nirmatrelvir;100 mg ritonavir presentation is designed to provide appropriate dosing for patients within the scope of this authorization with moderate renal impairment. See section 2.2 of the Fact Sheet for Healthcare Providers for more information.

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respectively, through Pfizer's website www.COVID19oralRX.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for PAXLOVID
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of PAXLOVID for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of PAXLOVID, when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that PAXLOVID (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of PAXLOVID under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), PAXLOVID is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer and Authorized Distributors[15]

A. Pfizer and authorized distributor(s) will ensure that PAXLOVID is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

[15] Supra at Note 11.

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B. Pfizer and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Pfizer and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving PAXLOVID. Pfizer will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Pfizer may request changes to this authorization, including to the authorized Fact Sheets for PAXLOVID. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[16]

E. Pfizer may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of PAXLOVID as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for PAXLOVID are prohibited. If the Agency notifies Pfizer that any instructional and educational materials are inconsistent with the authorized labeling, Pfizer must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

F. Pfizer will report to FDA all serious adverse events and medication errors potentially related to PAXLOVID use that are reported to Pfizer using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

[16] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

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Submitted reports under both options must state: "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Pfizer will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of PAXLOVID that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Pfizer must recall them.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Pfizer will manufacture PAXLOVID to meet all quality standards and per the manufacturing process and control strategy as detailed in Pfizer's EUA request. Pfizer will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under Condition D.

J. Pfizer will list each presentation of PAXLOVID with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

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K. Through a process of inventory control, Pfizer and authorized distributor(s) will maintain records regarding distribution of PAXLOVID (i.e., lot numbers, quantity, receiving site, receipt date).

L. Pfizer must provide the following information to the Agency:

1. Pfizer will 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. Pfizer will conduct these surveillance activities on at least a monthly basis and submit reports to FDA on these surveillance activities on a quarterly basis. In these reports, Pfizer will 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).
2. Pfizer will also 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. Pfizer will 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.

M. Pfizer shall provide samples as requested of the authorized nirmatrelvir to HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s) or target cleavage sites) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized nirmatrelvir may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

N. Pfizer and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom PAXLOVID Is Distributed and Healthcare Providers Administering PAXLOVID

O. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of PAXLOVID.

P. Healthcare facilities and healthcare providers receiving PAXLOVID will track all serious adverse events and medication errors that are considered to be potentially related to PAXLOVID use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-

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800-FDA-1088 for questions. Submitted reports must state, "PAXLOVID use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 must also be provided to Pfizer per the instructions in the authorized labeling.

Q. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

R. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of PAXLOVID for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

S. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Pfizer and/or FDA. Such records will be made available to Pfizer, HHS, and FDA for inspection upon request.

T. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

U. All descriptive printed matter, advertising, and promotional materials relating to the use of PAXLOVID under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling", or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of PAXLOVID under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

V. Pfizer may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of PAXLOVID that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized

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in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Pfizer may not imply that PAXLOVID is FDA-approved for its authorized use in the pediatric patient population as detailed in the Scope of Authorization (Section II) by making statements such as "PAXLOVID is safe and effective for the treatment of COVID-19 in pediatric patients."

W. All descriptive printed matter, advertising, and promotional material, relating to the use of PAXLOVID under this authorization clearly and conspicuously shall state that:

- PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death; and
- The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Pfizer that any descriptive printed matter, advertising, or promotional materials do not meet the terms set forth in Conditions U through W of this EUA, Pfizer must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

_____

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Document 2C.8

U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19

Document URL

https://www.fda.gov/media/155052/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

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Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19

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Questions related to Paxlovid's approval or EUA

Q: Is Paxlovid FDA-approved to treat or prevent COVID-19?

A. On May 25, 2023, FDA approved a New Drug Application (NDA) for Paxlovid for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has determined Paxlovid is safe and effective when used in accordance with the FDA-approved labeling.

Paxlovid is not FDA-approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q. Now that Paxlovid is an approved drug, is the EUA continuing, and what does the EUA authorize?

A. Yes. The EUA authorizes the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

The EUA continues to authorize Paxlovid for emergency use to treat certain eligible pediatric patients, a patient population that is not covered under the approved NDA for Paxlovid at this time. Paxlovid also remains authorized under EUA to ensure continued access for all eligible patients to the U.S. government's supply of Paxlovid, including adult patients who are the subject of the approved NDA, pending commercial launch of the approved product.

Paxlovid is not authorized:

- for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- for use longer than five consecutive days.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. Does the authorized Paxlovid provide the same clinical benefit as the approved Paxlovid, once the approved Paxlovid is available?

A. Yes. The authorized Paxlovid contains the same tablets (nirmatrelvir tablets and ritonavir tablets) as the Paxlovid that is now FDA-approved. Since Paxlovid was initially authorized for emergency use, Pfizer has also been required, as a condition under the EUA, to comply with the same good manufacturing practices that apply to approved products. Based on these considerations, it is FDA's expectation that patients being treated with Paxlovid for COVID-19 will receive the same clinical benefit as long as the product is used in accordance with the labeling, regardless of whether the authorized or approved Paxlovid is dispensed.

Paxlovid is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults. Paxlovid is authorized for emergency use, but not FDA-approved, for the treatment of mild-to-moderate COVID-19 in certain pediatric patients.

Q. Why does the EUA authorize Paxlovid for its approved patient population, specifically for the treatment of mild-to-moderate COVID-19 in high-risk adults?

A. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of this EUA. To ensure continued access to the U.S. government's supply for Paxlovid and fully meet the public health need before commercial launch of the approved product, the EUA continues to include the patient population now approved under the NDA for Paxlovid.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. May health care providers prescribe Paxlovid for uses not authorized under EUA?

A. At this time, the U.S. government continues to oversee the distribution of Paxlovid, which consists solely of Paxlovid that is labeled and packaged in accordance with the EUA. The Letter of Authorization for the EUA provides for the use of Paxlovid only when consistent with the terms and conditions of the authorization. Paxlovid is currently authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Although Paxlovid has been approved for use in eligible adult patients who are also included in the EUA population, the approved product has not yet commercially launched.

In certain circumstances, Paxlovid labeled and packaged in accordance with the EUA may also be accessed through an Expanded Access Investigational New Drug Application, also referred to as "compassionate use", for uses not within the scope of the EUA for Paxlovid, as appropriate. Expanded access may be considered when **all** of the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Health care providers seeking to obtain Paxlovid under expanded access should first contact Pfizer through its website.

Once Pfizer has provided the requisite authorization, health care providers should contact FDA using the information detailed below to complete the process:

- During normal business hours (8:00 a.m. – 4:30 p.m. ET, weekdays):
  - By phone – (301) 796-3400 or (855) 543-3784

- By email – DDI.EIND@fda.hhs.gov
- Outside of normal business hours (After 4:30 p.m. ET weekdays and all day on weekends/federal holidays)
  - By phone – (301) 796-9900
  - By email – CDER-EIND@fda.hhs.gov

General information on expanded access for providers and patients, respectively, can be found on FDA's website.

Q. Paxlovid is approved and authorized only for certain patients at "high risk". What does "high risk" mean?

A. Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment with COVID-19 and that patient's medical history.

Resources providing information on conditions that place a patient with mild-to-moderate COVID-19 at high risk for disease progression, including hospitalization or death, can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. Why is pediatric use not approved for Paxlovid and only authorized under the EUA?

A. The clinical development of Paxlovid for pediatric use is ongoing.

Q. How can Paxlovid be obtained for use under the EUA?

A. For questions on how to obtain Paxlovid, please contact COVID19therapeutics@hhs.gov. Information about Paxlovid's distribution can be found here.

Efficacy and Safety Considerations

Q. Are there data showing the benefit of Paxlovid for treatment of mild-to-moderate COVID-19 for certain patients?

A. Yes. The primary data supporting the approval as well as the EUA for Paxlovid are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. The main outcome measured in the trial was the proportion of people who were hospitalized due to COVID-19 or died due to any cause during 28 days of follow-up. Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause through 28 days of follow-up by 86% compared to placebo among patients treated within five days of symptom onset and who did not receive COVID-19 therapeutic monoclonal antibody treatment.

In this analysis, 977 patients received Paxlovid, and 989 patients received placebo, and among these patients, 0.9% who received Paxlovid were hospitalized due to COVID-19 or died from any cause during 28 days of follow-up compared to 6.5% of the patients who received placebo. Of the people who received Paxlovid, no patients died through 24 weeks after receipt compared to 15 people who received placebo.

Details on the clinical trial results can be found in Section 14 of the authorized Fact Sheet for Health Care Providers and approved Prescribing Information.

Q. Are there data supporting the benefit of Paxlovid for high-risk patients with mild-moderate COVID-19 regardless of prior/acquired immunity?

A. Benefit of Paxlovid was observed in patients with prior immunity to the virus that causes COVID-19. Among patients in EPIC-HR who were antibody positive at trial enrollment, the risk of COVID-19-related hospitalization or death from any cause during 28 days of follow-up was 0.2% among those treated with Paxlovid compared with 1.7% of those receiving placebo. EPIC-SR was another clinical trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19. Among these vaccinated patients, there was a reduction in the risk of COVID-19 related hospitalization or death from any cause with use of PAXLOVID versus placebo, although not statistically significant.

Q. Does Paxlovid retain activity against currently circulating Omicron variants?

A. Yes. Based on virology data, Paxlovid retains activity against currently circulating Omicron variants.

Q. Does Paxlovid cause COVID-19 rebound?

A. EPIC-HR, described above, and EPIC-SR, another trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19 or unvaccinated patients with no risk factors for progression to severe COVID-19, were both randomized placebo-controlled trials. These trials provide useful data to assess COVID-19 rebound. Data from these two trials showed that rebound in SARS-CoV-2 (RNA or virus) shedding or self-reported COVID-19 symptoms occurred in a subset of patients and happened at similar rates in both the patients receiving Paxlovid and placebo. Based on the data currently available to FDA, there is not a clear association between Paxlovid treatment and COVID-19 rebound.

Q. Are there potential side effects of Paxlovid?

A. Yes. Paxlovid consists of nirmatrelvir and ritonavir, and ritonavir interacts with many other medicines, which may lead to serious or life-threatening adverse reactions. Patients should tell their health care providers all of the medicines they are taking, including over-the-counter medications and herbal supplements, when deciding whether to take Paxlovid.

Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved Prescribing Information and authorized Fact Sheet for Health Care Providers for the Paxlovid EUA include a boxed warning with instructions for providers to review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

The most common side effects of taking Paxlovid include impaired sense of taste (for example, a metallic taste in the mouth) and diarrhea.

Liver problems have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Patients should talk with their health care provider if they have a history of liver problems.

Paxlovid is not recommended for patients with severe kidney problems, and a different dose is needed for patients with moderate kidney problems. Patients should talk with their health care provider if they have a history of kidney problems.

See Warnings and Precautions in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers for additional information on risks associated with Paxlovid.

Q. Why was a boxed warning included in the Paxlovid prescribing information?

A. Paxlovid includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain other medications the patient may be taking, resulting in potentially severe, life-threatening, or fatal events due to drug-drug interactions. Such interactions can be avoided by appropriate handling of the patient's other medications when starting treatment with Paxlovid or, in some situations when adjustments of the patient's other medication may not be feasible, choosing an alternative COVID-19 treatment for the individual patient. Since the authorization of Paxlovid under EUA, FDA has reviewed new data related to the risk of drug-drug interactions. These data were discussed by FDA during the recent Antimicrobial Drugs Advisory Committee on March 16, 2023.

- FDA identified more than 250 cases of serious adverse events assessed as possibly or probably related to Paxlovid drug-drug interactions. Many of these cases reported hospitalization, and a fatal outcome was reported in a few cases.
- FDA determined that greater than 50% of Paxlovid-eligible Medicare and VA patients were taking medications that were identified as having a drug-drug interaction with Paxlovid. FDA noted that most of these potential drug-drug interactions could be prevented or managed with dose modification, interruption, and/or additional monitoring.
- FDA determined that most Paxlovid prescriptions were written by a broad range of health care providers, who may not be familiar with managing potential drug-drug interactions associated with ritonavir, which is more commonly prescribed by infectious disease physicians and other specialists who may have more experience managing ritonavir drug-drug interactions.

Drug-drug interactions are not unique to Paxlovid and are almost always manageable risks. Prior to prescribing Paxlovid, health care providers must: 1) review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid and 2) determine if medications require a dose adjustment, interruption, and/or additional monitoring if taken at the same time as Paxlovid.

There are resources for health care providers to identify and manage potential drug-drug interactions with Paxlovid. These include: the approved prescribing information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions online checker.

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Provider Considerations When Prescribing Paxlovid

Q. Who may prescribe Paxlovid?

A. Paxlovid may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

Paxlovid may also be prescribed for an individual patient by a state-licensed pharmacist under certain conditions that are listed in the EUA. For more information on this topic, please refer to the section titled Questions for Pharmacist Prescribers below.

Q. When should Paxlovid be administered to a patient?

A. Patients should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive Paxlovid. Paxlovid treatment should be initiated as soon as possible after diagnosis of COVID-19, even if symptoms are mild, and within five days after symptoms start.

More information about administration is available in the in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers.

Q: Is a positive result from a direct SARS-CoV-2 viral test required prior to prescribing Paxlovid to a patient who is at high risk for severe COVID-19?

A: No. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact) who develop signs and symptoms consistent with COVID-19 may be diagnosed by their health care provider as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, their health care provider may determine that treatment with Paxlovid for COVID-19 is appropriate if the patient reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Letter of Authorization for Paxlovid and the authorized Fact Sheet for Healthcare Providers.

The agency continues to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

Q. I am traveling soon. May I receive Paxlovid under the EUA prior to travel in case I become sick with COVID-19?

A. Individuals being considered for Paxlovid treatment must meet the eligibility requirements under the EUA at the time of prescription. Providers must determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, assess risk for disease progression, assess renal and hepatic function, and review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

Q. What if I have questions about the expiration date on the Paxlovid carton or container?

A. FDA has authorized an extension to the expiration date (shelf-life) for certain lots of Paxlovid. To find the extended expiration date, enter the lot number found on the side of the carton or bottom of the blister pack at this website or talk with the pharmacist or provider.

Information on the authorized shelf-life extensions for Paxlovid may also be found on FDA's website.

Questions for pharmacist prescribers

Q. Are pharmacists permitted to prescribe Paxlovid?

A. The EUA authorizes state-licensed pharmacists to prescribe Paxlovid for an individual patient, subject to the terms and conditions of the EUA (e.g., eligible patient populations), under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- Paxlovid is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Q. What do state-licensed pharmacist prescribers need to do to determine whether a patient may be eligible to receive Paxlovid?

A. State-licensed pharmacist prescribers have the same requirements as all other prescribers to assess an adult or pediatric patient (12 years of age and older weighing at least 40 kg), who is being considered for treatment with Paxlovid, to determine that they have a diagnosis of mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

A review of reported symptoms should be completed to determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, and not severe COVID-19. Patients reporting

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shortness of breath or difficulty breathing should be immediately referred for further medical assessment to determine whether their illness has progressed to the severe stage, which may require hospitalization. Paxlovid is not authorized or approved for the treatment of severe COVID-19.

Definitions for mild and moderate illness are provided in NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

State-licensed pharmacist prescribers may determine whether an individual patient is at high risk for severe COVID-19 by obtaining a medical history from the patient or by accessing the patient's medical records. Resources about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. How do state-licensed pharmacist prescribers assess for potential drug interactions?

A. All prescribers are expected to utilize available health records or patient history to obtain a complete list of all medications (prescribed and non-prescribed) that the patient is taking. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain a comprehensive list of medications the patient is taking. Resources to identify potential drug interactions include the approved Prescribing Information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions.

Should an adjustment to another medication be needed due to a potential drug interaction, the state-licensed pharmacist should refer the individual patient for clinical evaluation with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Q. How do state-licensed pharmacist prescribers assess renal and hepatic function?

A. State-licensed pharmacist prescribers must have access to sufficient information from health records to assess renal and hepatic function. Health records include access to an electronic health record system containing this information in progress notes or laboratory records, reviewing a printed health record such as a laboratory report provided by the patient, or reviewing information in electronic health records the patient may have access to through a phone app or other means. Health records within the past 12 months are generally acceptable, provided there is no patient self-report or other information suggestive of kidney or liver disease. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain this information. If sufficient information is not available to assess renal and hepatic function, the state-licensed pharmacist should refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Physicians, advanced practice registered nurses, and physician assistants may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal

impairment. These providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis.

Q. Will state-licensed pharmacists be able to prescribe both the standard and renal doses of Paxlovid?

A. Yes, the EUA authorizes state-licensed pharmacists to prescribe both the standard and renal doses of Paxlovid, subject to the terms and conditions on pharmacist prescribing as detailed in the EUA, provided the pharmacist has adequate information to assess renal function and the patient is otherwise eligible to receive Paxlovid.

General EUA-related questions

Q. What is an emergency use authorization (EUA)?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?

A. Yes. As part of the EUA, FDA requires health care providers who prescribe Paxlovid to report all medication errors and serious adverse events considered to be potentially related to Paxlovid through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Pfizer.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Q. Do patient outcomes need to be reported under the EUA?

A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Paxlovid occurring during treatment is required.

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Q. FDA has issued a number of EUAs including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?

A. As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities Guidance, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?

A. Under the authorization, Pfizer must make available the authorized Fact Sheets on its website at: www.COVID19oralRX.com. Health care facilities and health care providers must ensure that fact sheets are made available to patients, parents, and caregivers through "appropriate means" and electronic delivery of the Fact Sheet is an appropriate means.

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Document 2C.9

U.S. FDA Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers

Document URL

https://www.fda.gov/media/158165/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

Not applicable

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PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

This checklist is intended as an aid to support clinical decision making for prescribers. However, use of this checklist is not required to prescribe PAXLOVID under the EUA.

Medical History

- ❑ Has mild to moderate COVID-19[1]
- ❑ Age ≥ 18 years OR ≥ 12 years of age and weighing at least 40 kg
- ❑ Has one or more risk factors for progression to severe COVID-19[2]
- ❑ Symptom onset within 5 days (Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by [insert date]. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.)
- ❑ Not requiring hospitalization due to severe or critical COVID-19 at treatment initiation
- ❑ No known or suspected severe renal impairment (eGFR ≤ 30 mL/min)
    - Note that a dose reduction is required for patients with moderate renal impairment (eGFR ≥30-<60 mL/min); see the Fact Sheet for Healthcare Providers.
    - To assess renal function:
        - Physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under state law to prescribe drugs may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal impairment. Providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis based on history or exam.
        - State-licensed pharmacists must have sufficient information available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient; see the Fact Sheet for Healthcare Providers.
- ❑ No known or suspected severe hepatic impairment (Child-Pugh Class C)
    - To assess hepatic impairment:
        - Physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under state law to prescribe drugs may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of hepatic impairment.
        - State-licensed pharmacists must have sufficient information available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient; see the Fact Sheet for Healthcare Providers.

[1] https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Patients%20with%20mild%20illness%20may,on%20exertion%2C%20or%20abnormal%20imaging

[2] Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment of COVID-19 and that patient's medical history. For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

❑ No history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to the active ingredients (nirmatrelvir or ritonavir) or other components of the product

NOTES: _____

Concomitant Medications

NOTE: The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if:

- Sufficient information is not available to assess for a potential drug interaction
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

See the Fact Sheet for Healthcare Providers for the full Limitations of Authorized Use.

❑ HMG-CoA reductase inhibitors (statins)

- *If the patient is taking lovastatin or simvastatin*, which are contraindicated with PAXLOVID coadministration, PAXLOVID can be given if the statin can be held 12 hours prior to the first dose of PAXLOVID treatment, held during the 5 days of treatment, and restarted 5 days after completing PAXLOVID.
- *If the patient is taking atorvastatin or rosuvastatin*, consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.

❑ Hormonal contraceptives containing ethinyl estradiol*: If the patient is taking a hormonal contraceptive containing ethinyl estradiol*, consider an additional non-hormonal method of contraception during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.

❑ Medications for HIV-1 Treatment: *If the patient is taking medications for the treatment of HIV-1 infection*, with the exception of maraviroc[3], HIV antiretroviral medications can be co-administered with PAXLOVID without dose adjustment, but arranging follow-up by the HIV care provider to monitor for side effects is recommended.[4,5,6]

[3] Please see the maraviroc prescribing information here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022128Orig1s019,208984Orig1s002lbl.pdf

[4] Exposure of certain HIV medications may be altered with PAXLOVID co-administration.

[5] Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

[6] PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

- ❑ Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID
  - ❑ Patient is not taking any other medications
  - ❑ Patient is not taking any of the medications listed below.
    - In addition, the patient's other medications have been checked for contraindications, the need for dose adjustment, or increased monitoring due to drug interactions with a strong CYP3A inhibitor such as ritonavir based on appropriate resources such as the prescribing information of these medications.
  - ❑ Patient is NOT taking any of the medications listed in RED but is taking one or more of the medications listed below in YELLOW, and dose adjustment, holding of medication, or increased monitoring is planned (additional resources which include instructions for managing specific drug interactions are included at the end of this document).
    - In addition, the patient's other medications not listed below have been checked for contraindications, the need for dose adjustment, or increased monitoring due to drug interactions with a strong CYP3A inhibitor such as ritonavir based on appropriate resources such as the prescribing information of these medications.

    NOTES: _____

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID (listed alphabetically by generic name)

Interaction Codes:

XXX — Coadministration of this drug with PAXLOVID is CONTRAINDICATED. For further information, refer to the Fact Sheet for Healthcare Providers and the individual Prescribing Information for the drug.

*** — Coadministration of this drug with PAXLOVID should be avoided and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary. Consultation with the prescriber of the potentially interacting drug is recommended. For further information, refer to the Health Care Provider Fact Sheet and the individual Prescribing Information for the drug.

The table below provides a listing of clinically significant drug interactions, including contraindicated drugs, in addition to those listed under Concomitant Medications above (HMG-CoA reductase inhibitors [statins], hormonal contraceptives containing ethinyl estradiol, and medications for HIV-1 treatment). ***Drugs listed in this table are a guide and are not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.***

Drug	Drug Class	Interaction Code
abemaciclib	Anticancer drug	***
alfuzosin	Alpha 1-adrenoreceptor antagonist	XXX
aliskiren	Cardiovascular agent	***
amiodarone	Antiarrhythmic	XXX
amlodipine	Calcium channel blocker	***
apalutamide	Anticancer drug	XXX
apixaban	Anticoagulant	***
aripiprazole	Neuropsychiatric agent	***
avanafil	PDE5 inhibitor	***
bedaquiline	Antimycobacterial	***
betamethasone	Systemic corticosteroid	***
brexpiprazole	Neuropsychiatric agent	***
bosentan	Endothelin receptor antagonist	***
budesonide	Systemic corticosteroid	***
bupropion	Antidepressant	***

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PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
buspirone	Sedative/hypnotic	***
carbamazepine	Anticonvulsant	XXX
cariprazine	Neuropsychiatric agent	***
ceritinib	Anticancer drug	***
ciclesonide	Systemic corticosteroid	***
cilostazol	Cardiovascular agent	***
clarithromycin	Anti-infective	***
clonazepam	Anticonvulsant	***
clorazepate	Sedative/hypnotic	***
clopidogrel	Cardiovascular agent	***
clozapine	Antipsychotic	***
colchicine	Anti-gout	XXX
cyclosporine	Immunosuppressant	***
dabigatran	Anticoagulants	***
darifenacin	Muscarinic receptor antagonist	***
dasabuvir	Hepatitis C direct acting antiviral	***
dasatinib	Anticancer drug	***
dexamethasone	Systemic corticosteroid	***
diazepam	Sedative/hypnotic	***
digoxin	Cardiac glycoside	***
dihydroergotamine	Ergot derivative	XXX
diltiazem	Calcium channel blocker	***
disopyramide	Antiarrhythmic	***
dronedarone	Antiarrhythmic	XXX
elbasvir/grazoprevir	Hepatitis C direct acting antiviral	***
eletriptan	Migraine medication	XXX
elexacaftor/tezacaftor/ivacaftor	Cystic fibrosis transmembrane conductance regulator potentiator	***
encorafenib	Anticancer drug	***
eplerenone	Cardiovascular agent	XXX
ergotamine	Ergot derivative	XXX
erythromycin	Anti-infective	***
estazolam	Sedative/hypnotic	***
everolimus	Immunosuppressant	***
felodipine	Calcium channel blocker	***
fentanyl	Narcotic analgesic	***
finerenone	Mineralocorticoid receptor antagonist	XXX
flecainide	Antiarrhythmic	XXX
flurazepam	Sedative/hypnotic	***
fluticasone	Systemic corticosteroid	***
flibanserin	Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	XXX

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PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
glecaprevir/pibrentasvir	Hepatitis C direct acting antiviral	***
hydrocodone	Narcotic analgesic	***
ibrutinib	Anticancer drug	***
iloperidone	Neuropsychiatric agent	***
isavuconazonium sulfate	Antifungal	***
itraconazole	Antifungal	***
ivabradine	Cardiovascular agent	XXX
ivacaftor	Cystic fibrosis transmembrane conductance regulator potentiator	***
ivosidenib	Anticancer drug	***
ketoconazole	Antifungal	***
lidocaine (systemic)	Antiarrhythmic	***
lomitapide	Microsomal triglyceride transfer protein (MTTP) inhibitor	XXX
lumacaftor/ivacaftor	Cystic fibrosis transmembrane conductance regulator potentiator	XXX
lumateperone	Neuropsychiatric agent	***
lurasidone	Antipsychotic	XXX
meperidine	Narcotic analgesic	***
methadone	Narcotic analgesic	***
methylergonovine	Ergot derivative	XXX
methylprednisolone	Systemic corticosteroid	***
midazolam (administered parentally)	Sedative/hypnotic	***
midazolam (oral)	Sedative/hypnotic	XXX
mometasone	Systemic corticosteroid	***
naloxegol	Opioid antagonist	XXX
neratinib	Anticancer drug	***
nicardipine	Calcium channel blocker	***
nifedipine	Calcium channel blocker	***
nilotinib	Anticancer drug	***
ombitasvir/paritaprevir /ritonavir	Hepatitis C direct acting antiviral	***
oxycodone	Narcotic analgesic	***
phenobarbital	Anticonvulsant	XXX
phenytoin	Anticonvulsant	XXX
pimavanserin	Neuropsychiatric agent	***
pimozide	Antipsychotic	XXX
primidone	Anticonvulsant	XXX
propafenone	Antiarrhythmic	XXX
quetiapine	Antipsychotic	***
quinidine	Antiarrhythmic	XXX
ranolazine	Antianginal	XXX
rifabutin	Antimycobacterial	***
rifampin	Antimycobacterial	XXX

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PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Drug	Drug Class	Interaction Code
rifapentine	Antimycobacterial	XXX
rimegepant	Migraine medication	***
riociguat	sGC stimulator	***
rivaroxaban	Anticoagulant	***
salmeterol	Long-acting beta-adrenoceptor agonist	***
saxagliptin	DPP4 inhibitor	***
Sildenafil (when used for erectile dysfunction)	PDE5 inhibitor	***
sildenafil (Revatio®) when used for pulmonary arterial hypertension	PDE5 inhibitor	XXX
silodosin	Benign prostatic hyperplasia agent	XXX
sirolimus	Immunosuppressant	***
sofosbuvir/velpatasvir/ voxilaprevir	Hepatitis C direct acting antiviral	***
St. John's Wort (hypericum perforatum)	Herbal product	XXX
suvorexant	Neuropsychiatric agent	***
tacrolimus	Immunosuppressant	***
tadalafil	PDE5 inhibitor	***
tamsulosin	Alpha 1-adrenoreceptor antagonist	***
tezacaftor/ivacaftor	Cystic fibrosis transmembrane conductance regulator potentiator	***
ticagrelor	Cardiovascular agent	***
tofacitinib	JAK inhibitor	***
tolvaptan	Vasopressin receptor antagonist	XXX
trazodone	Antidepressant	***
triamcinolone	Systemic corticosteroid	***
triazolam	Sedative/hypnotic	XXX
ubrogepant	Migraine medication	XXX
upadacitinib	JAK inhibitor	***
vardenafil	PDE5 inhibitor	***
venetoclax	Anticancer drug	***
verapamil	Calcium channel blocker	***
vinblastine	Anticancer drug	***
vincristine	Anticancer drug	***
voclosporin	Immunosuppressant	XXX
vorapaxar	Cardiovascular agent	***
voriconazole	Antifungal	***
warfarin	Anticoagulant	***
zolpidem	Sedative/hypnotic	***

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

ADDITIONAL RESOURCES:

PAXLOVID - Fact Sheet for Healthcare Providers: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

Prescribing Information (Label/Package Insert) for Individual Drugs (Drugs@FDA): https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

University of Liverpool COVID-19 Drug Interactions: https://www.covid19-druginteractions.org/checker

NIH COVID-19 Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

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Document 2C.10

Pfizer Important Prescribing and Dispensing Information (April 5, 2022)

Document URL

https://www.fda.gov/media/155071/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

Not applicable

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August 05, 2022

IMPORTANT PRESCRIBING AND DISPENSING INFORMATION

Subject: Minimizing wrong dose medication errors and revised Patients, Parents and Caregivers Fact Sheet for PAXLOVID (nirmatrelvir tablets; ritonavir tablets).

Dear Healthcare Provider,

The purpose of this letter is to make you aware of wrong-dose medication errors associated with PAXLOVID (nirmatrelvir tablets; ritonavir tablets), provide a reminder about the two PAXLOVID dose packs and inform you of the availability of a revised PAXLOVID Patients, Parents and Caregivers Fact Sheet (PFS) to be dispensed with each PAXLOVID prescription.

Pfizer has become aware of reports of wrong-dose medication errors that have occurred with Paxlovid. These wrong-dose errors have occurred during prescribing, dispensing, and administration. Many of these errors have occurred during patient self-administration and generally involved patients incorrectly taking the wrong combination of nirmatrelvir tablets and ritonavir tablets from the blister card leading to wrong-dose medication errors.

Pfizer has revised the PAXLOVID Patients, Parents and Caregivers Fact Sheet to address wrong dose medication errors that occur during patient self-administration. The revised Fact Sheet will show how the medication is labeled and inform the patient on how to correctly take Paxlovid. Each dispensed prescription for Paxlovid should include a Patients, Parents and Caregivers Fact Sheet.

As a reminder, PAXLOVID contains two different drugs (nirmatrelvir tablets and ritonavir tablets) that are co-packaged in a daily blister card for oral use.

PAXLOVID is available in the following two packaging configurations.

1. **300 mg; 100 mg Dose Pack:** This packaging configuration should be used for patients with normal renal function or mild renal impairment (eGFR* ≥60 ml/min).

   The 300 mg; 100 mg Dose Pack is a carton containing 5 daily blister cards. Each blister card contains a daily morning dose and evening dose, with each dose consisting of **300 mg nirmatrelvir** (two oval, pink 150 mg tablets) and **100 mg ritonavir** (one white to off-white film-coated 100 mg tablet).

2. **150 mg; 100 mg Dose Pack:** This packaging configuration should be used for patients with **moderate renal impairment** (eGFR ≥30 to <60 mL/min).

   The 150 mg; 100 mg Dose Pack is a carton containing 5 daily blister cards. Each blister card contains a daily morning dose and evening dose, with each dose consisting of **150 mg nirmatrelvir** (one oval, pink 150 mg tablet) and **100 mg ritonavir** (one white to off-white film-coated 100 mg tablet).

PAXLOVID is not recommended in patients with severe renal impairment (<30 mL/min) as the appropriate dose has not been determined.

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PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) as no pharmacokinetic or safety data is available in subjects with severe hepatic impairment.

*eGFR=estimated glomerular filtration rate based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula

HEALTHCARE PROVIDER ACTIONS:

- Use the PAXLOVID **150 mg; 100 mg** Dose Pack only when prescribing or dispensing PAXLOVID for patients with **moderate renal impairment** (eGFR ≥30 to <60 mL/min).
- When prescribing PAXLOVID, always specify the numeric dose for each active ingredient within PAXLOVID as follows:
    - PAXLOVID 300 mg; 100 mg Dose Pack- 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir for patients with normal renal function or mild renal impairment, or
    - PAXLOVID 150 mg; 100 mg Dose Pack- 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment (eGFR ≥30 to <60 mL/min)

- **Always dispense the most recent version of Patients, Parents and Caregivers Fact Sheet with each prescription**.

- Counsel patients on how the medication is labeled on the blister pack, and teach them about the two different medications that they will be taking twice a day

- Stay current with the latest EUA Fact Sheet for Healthcare Providers (www.COVID19oralRx.com)

Emergency Use Authorization (EUA):

PAXLOVID has not been approved but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death.

The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Healthcare providers should consider the benefit-risk for an individual patient.

Limitations of Authorized Use:

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

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PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

Reporting Adverse Events and Medication Errors:

Under the EUA, all serious adverse events and medication errors potentially related to PAXLOVID use must be reported within 7 calendar days from the healthcare provider's awareness of the event.

Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.
- Please provide a copy of all FDA MedWatch forms to Pfizer via fax (1-866-635-8337), telephone (1-800-438-1985) or website www.pfizersafetyreporting.com

The PAXLOVID EUA Fact Sheet for Healthcare Providers is available at www.COVID19oralRx.com or by scanning the QR Code below:

Sincerely,
Eddie G M Power PhD MBA GFMD
Vice President, North America Medical Affairs

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Document 2C.11

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 23, 2022)

Document URL

https://www.fda.gov/media/159987/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

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Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)[1]	000105
Date of Memorandum	February 23, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Integrated Review Completion Date for Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)

[1] If a pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Rationale for Revisions to EUA Fact Sheets

The PAXLOVID EUA factsheets are being revised at this time for the following reasons:

1. **To add information regarding the post-authorization report of cases of hypersensitivity reactions in association with PAXLOVID use.**

   The label for Norvir (ritonavir 600 mg po bid used as chronic therapy as a component HIV treatment) contains a Warning and Precaution about allergic reactions that states the following:

   - *Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.*

   This Warning and Precaution was not included in the PAXLOVID Fact Sheet with the original authorization because no signal for hypersensitivity reactions was seen in the PAXLOVID clinical trials and because it was unclear if hypersensitivity reactions would be seen with the lower ritonavir dose and shorter duration administered as part of PAXLOVID.

   However, in late January 2022, DAV was made aware of four FAERS reports regarding clinically significant hypersensitivity reactions during or after PAXLOVID treatment; three additional cases through February 7, 2022, for a total of seven cases, were discovered after subsequent communications with the Sponsor. In addition, fifteen cases were reported describing skin-related symptoms without swelling or shortness of breath that are also possible hypersensitivity reactions. These reports are summarized in Table 1 and Table 2 below.

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Table 1. Summary of Reports for Clinically Significant Hypersensitivity Reactions

FAERS #/ Country	Age/Sex	Symptom(s)	Onset	Intervention	Outcome	Concomitant meds reported
20306799 US	67 F	Urticaria, pruritus, facial swelling	After third dose	Discontinued drug	Symptoms subsided after 10+ hours	Yes (no treatment dates)
20334069 US	70 F	Tongue swelling, lip tingling	After first dose (worse after second dose)	Advised to discontinue drug	Unknown	No
20334125 US	66 M	Tongue swelling, sore throat, chest pain, dyspnea, increased BP	After second dose	Discontinued drug	Symptoms resolved	Yes (none recently started)
20347548 US	80 F	Dyspnea, possible laryngeal edema	After first dose	Unknown	Unknown	No
20378409, 20387833 US	72 F	Lip tingling, tongue swelling	First day	Unknown	Unknown	No
ToxIC Report* 925 US	56 M	Chest discomfort, dyspnea, nausea	After first dose	Discontinued drug	Symptoms resolved	Yes (no concomitant medications)
20416823, 20432809 US	77 M	Dysphagia, oropharyngeal pain, throat tightness	After second dose	Unknown	Unknown	No

Abbreviations: F, female; M, male.
*This case was not from FAERS but from the ToxIC Registry, a multi-center toxico-surveillance and research network overseen by the American College of Medical Toxicology.

Table 2. Summary of FAERS Reports for Other Rash Adverse Events

FAERS #/ Country	Age/Sex	Symptom(s)	Onset (day of treatment)	Intervention	Outcome
20334070 US	50 M	Blisters on lips and nostrils	2	Discontinued drug	Symptoms resolved
20334126	81	Full body rash	2	Unknown	Unknown

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US	M				
20346759, 20359786 US	Unknown	Rash on inside of leg	Unknown	Unknown	Unknown
20391329 US	56 M	Blotching/discoloration under forearm, inner bicep, around thighs/calves	1	Discontinued drug.	Unknown
20391535 US	36 F	Rash and “bumps”	1	Cortisone cream, diphenhydramine advised	Unknown
20407351 US	17 F	Facial rash	1	Discontinued drug, diphenhydramine recommended	Unknown
20405987 US	20 F	Hives on hands	Unknown	Unknown	Unknown
20378790 US	31 F	Facial erythema	1	Unknown	Unknown
20351314 US	38 F	Rash, itching	4	Unknown	Unknown
20430212, 20440887 US	63 F	Rash on knuckles, wrist, elbows, knees and itching	10	Unknown	Unknown
20391154 US	48 F	Erythema of body, itchy	2	Diphenhydramine, prednisone	Unknown
20379637 US	79 F	Itchy skin	5	Unknown	Unknown
20415615, 20416840 US	60 F	Pruritus	1	Discontinued drug, dexamethasone and prednisone ordered	Unknown
20415968 US	69 M	Itching	3	Unknown	Unknown
20363122 US	45 F	Itching	Unknown	Discontinued drug	Unknown

Abbreviations: F, female; M, male.

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The review team finds that these cases are suggestive of PAXLOVID-associated hypersensitivity reactions. Most events occurred after the first, second, or third dose, and the few cases with a known outcome reported resolution of symptoms after PAXLOVID was discontinued. Notably, some of the cases in Table 1 were suggestive of anaphylaxis. Therefore, the review team recommends the addition of a Warning and Precaution to the PAXLOVID Fact Sheet for Health Care Providers and that the risk of hypersensitivity reactions be described in the PAXLOVID Fact Sheet for Patients.

There was one additional case (FAERS #20432313), not included in the tables because additional information is pending, in which a patient had a multifocal reaction similar to Stevens-Johnsons involving the mucosa (mouth sores and irritated eyes) and multiples sores on his body (described as "some larger than a golf ball") that began within 10 days of starting PAXLOVID. As both toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have been reported with ritonavir, the warning and precaution will include that these serious hypersensitivity reactions have been reported with components of PAXLOVID.

2. **To revise the drug interactions to remove piroxicam from Contraindications (Section 4) and from Established and Other Potentially Significant Drug Interactions (Table 1 in Section 7.3).**

The Sponsor listed piroxicam as a contraindicated drug in the Phase 2/3 clinical trials and in the PAXLOVID Fact Sheet and as a drug with established and other potentially significant drug interactions in the PAXLOVID Fact Sheet. This interaction is based on its inclusion in the Norvir 100mg SmPC [Norvir 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)] which states that concomitant use of ritonavir and piroxicam leads to increased piroxicam plasma concentration and thereby increased risk of serious respiratory depression or hematologic abnormalities or other serious adverse effects.

The review team requested a rationale for the continued inclusion of this interaction in the Fact Sheet. The current piroxicam labeling lists CYP2C9 as the primary enzyme involved in the drug's metabolism. While ritonavir has the potential to induce CYP2C9, concomitant use with piroxicam would lead to decreased piroxicam plasma levels, not increased piroxicam plasma levels as noted in the Norvir SmPC and the Fact Sheet. Further, the piroxicam labeling does not include a clinical recommendation regarding coadministration with strong CYP3A4 inhibitors such as ritonavir. Thus, the review team recommends deletion of this interaction if a reasonable rationale for its inclusion cannot be provided.

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The Sponsor responded that after further review of the Norvir (ritonavir) and Feldene (piroxicam) package inserts, they agree with the deletion of piroxicam from the list of contraindicated drugs because a CYP3A4-based inhibitory interaction is unlikely to occur as piroxicam is mainly metabolized by CYP2C9.

3. **To update the reporting requirements for serious adverse events in Sections 6.4 and 6.5 for consistency with other Fact Sheets.**

Summary of Fact Sheet Revisions:

- The following Warning and Precaution was added to the Healthcare Provider Fact Sheet:

  5.2 Allergic Reactions/Hypersensitivity

  Hypersensitivity reactions have been reported with PAXLOVID including urticaria, angioedema, dyspnea, mild skin eruptions, and pruritus. Cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with components of PAXLOVID (refer to NORVIR labeling). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

- Section 6 of the Healthcare Provider Fact Sheet was revised to update the language in Section 6.4 (Required Reporting for Serious Adverse Events and Medication Errors) and to add the following sections:

  6.2 Post-Authorization Experience

  The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

  Immune System Disorders: Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

  6.5 Other Reporting Requirements

  Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

- Sections 4 and 7.3 were revised to remove piroxicam from the list of contraindicated medications and from the list of established and other potentially significant drug interactions.

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- Section 17 of the Healthcare Provider Fact Sheet (Patient Counseling Information) was also updated to include the following:

  Allergic Reactions/Hypersensitivity

  Inform patients that hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

- The Patient Fact Sheet was updated to include these new hypersensitivity safety events.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID.

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U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (March 18, 2022)

Document URL

https://www.fda.gov/media/159988/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Not applicable

Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	March 18, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets

The PAXLOVID EUA fact sheets are being revised at this time for the following reasons:

1. **To add recent nonclinical and clinical virology information to section 12.4.**

   Since the original PAXLOVID EUA in December 2021, additional virology data have become available including nirmatrelvir (NIR) activity against an expanded panel of SARS-CoV-2 variants (including Omicron), NIR resistance development in cell culture, and expanded SARS-CoV-2 sequencing analyses from the clinical trial EPIC-HR (C4671005). These new data were reviewed in detail in the virology review conducted by Dr. Patrick Harrington and Dr. Jonathan Rawson (please see their separate review in DARRTS) with their key conclusions provided below:

   - NIR retained activity (<2-fold change in mean EC_{50} value) against SARS-CoV-2 B.1.621 (Mu) and B.1.1.529 (Omicron) variants in cell culture. Five other independent studies have also found that NIR retains activity against the Omicron variants/sublineages B.1.1.529/BA.1, BA.1.1 and BA.2.

   - NIR resistance selection with mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A (G15 in SARS-CoV-2), T50K (L50 in SARS-CoV-2), P55L (E55 in SARS-CoV-2), F126L (Y126 in SARS-CoV-2), T129M (A129 in SARS-CoV-2), and/or S144A (S144 in SARS-CoV-2). The presence of the substitutions P55L and S144A was associated with reduced NIR susceptibility (~4-5-fold higher EC_{50} values). E55L alone did not affect NIR activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A led to significantly reduced NIR activity (91.9-fold higher K_i value).

   - Using recombinant SARS-CoV-2 viruses, the sponsor found that viruses containing Y54A and F140A Mpro substitutions could not be recovered, indicating that they result in a cell culture fitness defect. Virus containing the H172Y Mpro substitution was recovered only after multiple attempts and had a low titer, indicating a fitness defect. However, viruses containing S144A, E166A, and Q189K were recovered on the first attempt and had normal replication kinetics in A549-ACE2 cells. The sponsor will evaluate the susceptibility of these viruses to NIR.

   - Expanded analyses of SARS-CoV-2 sequencing data from clinical trial EPIC-HR (C4671005) revealed several Mpro amino acid substitutions that emerged in NIR/r treated subjects, including at previously identified amino acid positions potentially associated with NIR resistance, as well as at potentially novel resistance-associated positions. Of particular interest, an

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Mpro E166V substitution emerged in 3 NIR/r treated subjects (~1% of subjects with data; became predominant variant in 2 subjects). This position is in the NIR binding site and an E166A substitution was previously shown to confer 33-fold reduced NIR activity in a biochemical assay; the phenotypic impact of E166V is unknown. The previously noted Mpro position A260 again appeared to be a position where treatment-emergent substitutions were enriched in NIR/r treated subjects. Numerous other treatment-emergent Mpro amino acid substitutions are noted in the review and should continue to be monitored in clinical trials and characterized for their impact on NIR susceptibility in phenotypic assays.

- Certain amino acid substitutions at Mpro cleavage sites (CS) appeared to emerge preferentially in NIR/r treated subjects, particularly in CS#8 (nsp12/nsp13) and CS#10 (nsp14/nsp15). Treatment-emergent substitutions in one or both of these sites were detected in 15 (4%) NIR/r treated subjects and 3 (0.7%) placebo treated subjects. Among the NIR/r treated subjects there were no clear patterns of association between these treatment-emergent Mpro cleavage site amino acid substitutions and treatment-emergent Mpro amino acid substitutions. To our knowledge, no phenotypic data have been reported regarding the impact of amino acid changes in any Mpro cleavage site on SARS-CoV-2 susceptibility to NIR.

Based on the updated results and analyses summarized above, Section 12.4 Microbiology in the Fact Sheet for Healthcare Providers is being updated with new nonclinical and clinical virology information.

2. **To update the Fact Sheet for Healthcare Providers and the Patient Fact Sheet with the availability of an approved product for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.**

   At the time of the initial authorization for PAXLOVID, there were no approved products for the treatment of mild-to-moderate COVID-19. However, On January 21, 2022, the approved indication for remdesivir (trade name VEKLURY®) was expanded to include the treatment of non-hospitalized adult and pediatric patients (12 years of age and older and weighing at least 40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. The dosage is a loading dose of 200 mg remdesivir by intravenous (IV) infusion on Day 1 followed by once-daily maintenance doses of 100 mg remdesivir by IV infusion from Day 2. For the treatment of mild-to-moderate COVID-19 in outpatients, the total treatment duration is 3 days.

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The only approved alternative product to PAXLOVID is administered by IV infusion once daily for three days, which would be logistically challenging to implement for many healthcare centers, particularly given the infection control issues inherent in treating COVID-19 patients. Consequently, other products that are easier to administer are still needed for the treatment of mild-to-moderate COVID-19, and the EUA criteria for PAXLOVID are still met. However, the fact sheets are being updated to communicate the availability of an approved alternative product.

Summary of Fact Sheet Revisions:

- Section 12.4 of the Fact Sheet for Healthcare Providers was updated (1) to include new data on the antiviral activity of nirmatrelvir against an expanded panel of SARS-CoV-2 variants, (2) to add an additional Mpro amino acid substitution that emerged in a nirmatrelvir cell culture resistance selection study using MHV, and (3) to expand the listing of nirmatrelvir treatment-emergent Mpro and Mpro cleavage site amino acid substitutions detected in samples from clinical trial EPIC-HR (C4671005).

- Section 1 of the Fact Sheet for Healthcare Providers and the Patient Fact Sheet were amended to communicate the availability of the approved (though not adequate) alternative remdesivir.

    - In Section 1 of the Fact Sheet for Healthcare Providers, the text under "Information Regarding Available Alternatives for the EUA Authorized Use" now reads as follows:

      Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

      Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days).

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Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

- In the Patient Fact Sheet, the text under "What other treatment choices are there?" now reads as follows:

  Veklury (remdesivir) is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults and children. Talk with your doctor to see if Veklury is appropriate for you.

  Like PAXLOVID, FDA may also allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

  It is your choice to be treated or not to be treated with PAXLOVID. Should you decide not to receive it or for your child not to receive it, it will not change your standard medical care.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID.

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U.S. FDA Clinical Pharmacology EUA Summary Review (April 8, 2022)

Document URL

https://www.fda.gov/media/159989/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Clinical Pharmacology EUA Summary Review

EUA Number/SDN	105/90
Sponsor	Pfizer Inc.
Submission Date	March 11, 2022
OCP Reviewer	Cristina Miglis, PharmD, MS, BCPS
OCP Team Leader	Mario Sampson, PharmD
OCP Division/Office	Division of Infectious Diseases Pharmacology/Office of Clinical Pharmacology
OND Division/Office	Division of Antivirals/Office of Infectious Diseases
Drug Name	PAXLOVID (nirmatrelvir oral tablet co-packaged with ritonavir oral tablet)
Dosage and Administration	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
Indication	Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Rationale for Revisions to EUA Fact Sheets

The PAXLOVID EUA fact sheet was revised as follows:

1. Section 12.3 was edited to include summary data from two additional clinical studies that assessed the role of PAXLOVID as a perpetrator of drug-drug interactions. Study 1013 was a Phase 1, open-Label, 3-Treatment, 6-Sequence, 3-Period crossover study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of midazolam in healthy participants. The three treatment arms in this study included 1) a single oral dose of midazolam 2 mg, 2) multiple oral doses of PAXLOVID 300/100 mg in plus single 2 mg oral dose of midazolam and 3) multiple oral doses of ritonavir 100 + single 2 mg oral dose of midazolam. Midazolam plasma exposure based on geometric mean AUC_{inf} increased approximately 14-fold with a nearly 4-fold increase for C_{max} following co-administration with multiple oral doses of PAXLOVID.

   Study 1012 was a Phase 1, open-label, 3-treatment, 6-Sequence, 3-period crossover study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of dabigatran in healthy participants. Participants in this study received 1) dabigatran etexilate 75 mg as a single dose, 2) PAXLOVID 300 mg/100 mg q12h x 2 days plus 75 mg of dabigatran etexilate as a single dose on Day 2 and 3) Ritonavir 100 mg q12h x 2 days plus 75 mg of dabigatran etexilate as a single dose

on Day 2. Dabigatran plasma exposure based on geometric mean AUC_{inf} and C_{max} increased 1.9-fold and 2.3-fold respectively following co-administration with multiple doses of PAXLOVID.

Based on the results of these studies, we agree with the addition of Table 7 to the factsheet. Edits were also made to Table 2 to reflect that 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively.

2. The following edits were also made to Table 1 in Section 7.3.
    a. Dabigatran was added to the anticoagulants section to state increased dabigatran concentrations when coadministered with PAXLOVID. The clinical pharmacology review team recommended the following clinical comment based on the results of Study 1012 and specific recommendations on dose adjustments in the dabigatran product labeling: *Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information*.

    b. Additional instructions were added to the clinical comments for HMG-CoA reductase inhibitors. For lovastatin and simvastatin, instructions were added to discontinue the use of these statins during the five days of PAXLOVID treatment and for five days after completing PAXLOVID. This language expands on the previous factsheet recommendation to discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.

    The recommendation to discontinue the statin for five days after completion of PAXLOVID is based on the estimated time course of CYP3A recovery after stopping the enzyme inhibitor. In the publication by Stader et al, a modeling approach was used to evaluate the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir[1]. Lopinavir/ritonavir (400/100mg twice daily) was administered for 7 days in a virtual trial to achieve steady state CYP3A inhibition and the abundance of CYP3A was estimated for 21 consecutive days. The interaction potential after stopping lopinavir/ritonavir was investigated with midazolam (a CYP3A probe substrate) administered orally 5mg once daily starting on the seventh day. In all simulations conducted, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/ritonavir. While complete disappearance of CYP3A inhibition took 21 days, the amount of inhibition remaining after five days is not expected to be clinically significant for most drugs.

    In another publication by Hong et al, a physiologically based pharmacokinetic (PBPK) simulation-based approach was applied to predict the effect of ritonavir on the PK of elexacaftor-tezacaftor-ivacaftor (ETI) and determine a potential dose alteration of ETI to overcome the CYP3A inhibition mediated by ritonavir [2]. Steady-state PK of standard dose ETI alone and when co-administered with 100mg ritonavir twice daily for 5 days were

[1] Stader F., et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. Antimicrob Chemother 2020; 75: 3084–3086 doi:10.1093/jac/dkaa253 Advance Access publication 17 June 2020

[2] Hong et al. PBPK-led guidance for cystic fibrosis patients taking elexacaftor-tezacaftor-ivacaftor with nirmatrelvir-ritonavir for the treatment of COVID-19.

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simulated. A dose reduction of ETI during 5 days of ritonavir administration with resumption of full dose of ETI on day 9 (4 days after stopping ritonavir) provided a similar steady-state PK profile of the conventional regimen of ETI alone. Based on the data presented in these two studies, the clinical pharmacology review team recommends that patients on lovastatin or simvastatin wait for five days after completing PAXLOVID to resume statin therapy.

For atorvastatin and rosuvastatin, an additional sentence stating the statin does not need to be held prior to or after completing PAXLOVID was added. The Norvir label outlines specific clinical management strategies for these statins.

c. Additional instructions were added to the clinical comment for hormonal contraceptives to instruct patients and providers to consider an additional, non-hormonal method of contraception during the five days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID. This recommendation is based on the potential risk of reduced ethinyl estradiol exposure with ritonavir and is supported by data from the darunavir/ritonavir package insert[3] and a study by Kasserra et al [4], demonstrating a significant decrease in ethinyl estradiol exposure when coadministered with darunavir/ritonavir (600 mg/100 mg) for 14 days or 100 mg ritonavir for 10 days, respectively. While CYP enzymes are likely a contributor to this interaction, there are additional metabolic processes involved in ethinyl estradiol metabolism, including glucuronidation and sulfation. Based on the available data, it is unknown whether the magnitude of enzyme (CYP and non-CYP) induction after five days of PAXLOVID administration would be less compared to that observed with longer ritonavir dosing regimens of 10 to 14 days since the time course of induction of these additional metabolic processes has not been well characterized. Generally, contraceptive efficacy is attributed to progestin more than the estrogen component, however, potential loss of efficacy due to lower ethinyl estradiol exposure cannot be completely ruled out, since efficacy may be affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation, and endometrial lining changes. While the metabolism of progestin also relies on CYP3A, the relative contribution of CYP3A to the clearance of different progestins varies. Other metabolic enzymes, including CYP2C19, uridine 5'-diphospho- glucuronosyltransferases (UGTs), and sulfotransferases (SULTs), are also involved in the metabolism of certain progestins. As previously indicated, , the time course of these additional metabolic processes has not been well characterized.

Clinical Pharmacology Assessment

The review team's recommended revisions, as described above, were accepted by the applicant (with minor editorial revisions). The final agreed upon language is shown below:

[3] PREZISTA [package insert] Janssen Products; 2021.

[4] Kasserra et al. Effect of vicriviroc with or without ritonavir on oral contraceptive pharmacokinetics: a randomized, open-label, parallel-group, fixed-sequence crossover trial in healthy women. Clin Ther. 2011 Oct;33(10):1503-14.

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Edits to Table 1 in Section 7.3

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.

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Edits to Section 12.3

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
e. Determined by ^{19}F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution.

Table 7: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Co-administered Drug

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (5 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.
a. AUC=AUC_{inf} for both midazolam and dabigatran.
b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

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Document 2C.14

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (June 28, 2022)

Document URL

https://www.fda.gov/media/159724/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	June 28, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets and Other Documents

The PAXLOVID EUA Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents, and Caregivers; and Patient Eligibility Screening Checklist Tool for Prescribers are being revised at this time for the following reasons:

1. **To update the Fact Sheet for Healthcare Providers and the Patient Fact Sheet with post-authorization reports of abdominal pain, nausea, and malaise.**

   Since the original PAXLOVID EUA in December 2021, post-authorization reports have suggested the adverse events (AEs) of abdominal pain, nausea, and malaise may be associated with PAXLOVID use.

   - Abdominal Pain
     - Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that abdominal pain was associated with PAXLOVID use, with similar low rates reported among PAXLOVID and placebo recipients (≤1% of each group when pooling related terms). From the January 5, 2022, clinical study report for EPIC-HR, the following was reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively, for AEs with preferred terms (PTs) that could be categorized as abdominal pain:
       - abdominal pain PT: 2 (0.2%) versus 3 (0.3%) subjects
       - abdominal pain lower PT: 1 (0.1%) versus 0 subjects
       - abdominal pain upper PT: 3 (0.3%) versus 2 (0.2%) subjects
       - dyspepsia PT: 6 (0.5%) versus 5 (0.4%) subjects
     - Post-Authorization Cases: The Sponsor identified a total of 38 cases of abdominal pain with PAXLOVID use from their global safety database, of which 12 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, the Office of Surveillance and Epidemiology's Division of Pharmacovigilance (DPV) noted that abdominal pain was among the most commonly reported unlabeled adverse events with PAXLOVID use identified in the FDA Adverse Event Reporting System (FAERS).
     - Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), abdominal pain is included among the most frequently reported adverse drug reactions, with a reported frequency of 26%. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020659s072,022417s024,209512s007lbl.pdf).

   - Nausea

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- Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that nausea was associated with PAXLOVID use, with similar low rates reported among PAXLOVID and placebo recipients. From the January 5, 2022, clinical study report for EPIC-HR, the following was reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively:
  - Nausea PT: 16 (1.4%) versus 19 (1.7%)
  - Vomiting PT: 12 (1.1%) versus 9 (0.8%)
- Post-Authorization Cases: The Sponsor identified a total of 56 cases of nausea with PAXLOVID use from their global safety database, of which 23 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, DPV noted that nausea was among the most commonly reported unlabeled adverse events with PAXLOVID use identified in FAERS.
- Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), nausea and vomiting are each included among the most frequently reported adverse drug reactions, with reported frequencies of 57% and 32%, respectively.

- Malaise
  - Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that malaise was associated with PAXLOVID use. From the January 5, 2022, clinical study report for EPIC-HR, the following rates were reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively, for AEs with PTs similar to malaise (malaise specifically was not reported):
    - Asthenia PT: 3 (0.3%) versus 3 (0.3%)
    - Fatigue PT: 2 (0.2%) versus 5 (0.4%)
  - Post-Authorization Cases: The Sponsor identified a total of 67 cases of malaise with PAXLOVID use from their global safety database, of which 29 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, DPV noted that malaise and feeling abnormal were among the most commonly reported unlabeled adverse events with PAXLOVID use identified in FAERS.
  - Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), fatigue/asthenia is included among the most frequently reported adverse drug reactions, with a reported frequency of 46%.

The Sponsor proposed adding abdominal pain, nausea, and malaise to the Fact Sheet for Healthcare Providers under Section 6.2, Post-Authorization Experience, as well as to the other possible side effects in the PAXLOVID Fact

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Sheet for Patients, Parents, and Caregivers. Based on the post-authorization cases listed above combined with the frequent adverse drug reactions included in Norvir labeling, we agree with these additions.

2. **To update the drug-drug interaction information in the Fact Sheet for Healthcare Providers and the Patient Fact Sheet.**

   The original listing of drugs either contraindicated with PAXLOVID or with other clinically significant drug interactions with PAXLOVID was compiled by the Sponsor based on the NORVIR (ritonavir) US package insert, NORVIR 100 mg summary of product characteristics (SmPC), and KALETRA (lopinavir/ritonavir) US package insert. NORVIR was first approved in 1996, and Section 7.1 in the NORVIR label contains the following caveat about the listing of drugs that interact with ritonavir: "These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with ritonavir. The healthcare provider should consult appropriate references for comprehensive information." A similar caveat is included in the PAXLOVID Fact Sheet for Healthcare Providers; the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers; and the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers.

   However, some of the drugs that may interact with PAXLOVID, and which are not listed in the Fact Sheet for Healthcare Providers, may lead to serious adverse drug reactions. For example, a safety brief published by the Institute for Safe Medication Practices in May described a case of fatigue and bradycardia, with a heart rate below 40 beats per minute, that required evaluation and treatment in the emergency department, in a patient who was taking ivabradine and was prescribed PAXLOVID for COVID-19. Ivabradine is contraindicated with strong CYP3A inhibitors in the ivabradine prescribing information because strong CYP3A inhibitors increase ivabradine plasma concentrations and may exacerbate bradycardia and conduction disturbances; however, a potential drug interaction with ivabradine is not included in the NORVIR prescribing information nor the PAXLOVID fact sheets or checklist tool. Furthermore, PAXLOVID is more widely prescribed than NORVIR; NORVIR has been prescribed predominantly by HIV providers experienced with ritonavir drug interactions, which may not be the case for PAXLOVID. Finally, as the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers was developed as a resource for prescribers to help navigate what they should be checking when prescribing PAXLOVID and to minimize confusion about what is required under EUA, prescribers may not be aware, even with the caveat about the list not being comprehensive, that serious adverse drug reactions could occur due to interactions with drugs not included on the listing.

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Consequently, additional drugs are being added to the Fact Sheet for Healthcare Providers listing of contraindicated drugs in Section 4 and the listing of drugs with established and other potentially significant drug interactions in Table 1 in Section 7.3; these drugs either have listed drug reactions with strong CYP3A inhibitors in their prescribing information, are strong CYP3A inducers, are included as having drug interactions with ritonavir in the labeling of other ritonavir-containing products or in NORVIR labeling, or present a significant safety risk if omitted. For example, primidone, the label for which has not been updated to include pertinent drug-drug interaction data, was added to the list of contraindicated medications. The review team included this interaction in the fact sheet since 1) primidone is metabolized by CYP3A4 to the active metabolite phenobarbital, which is contraindicated with PAXLOVID and 2) primidone is included with phenobarbital as an example of a moderate clinical inducer for P450-mediated metabolisms for concomitant use clinical DDI studies and/or drug labeling. In addition, caveat language about the listed drugs being a guide and not a comprehensive list, that was already included in Section 7.3, is also being added to Sections 2.4 (Important Drug Interactions with PAXLOVID), 4 (CONTRAINDICATIONS), and 5.1 (Risk of Serious Adverse Reactions Due to Drug Interactions) for intentional redundancy to emphasize this point. Further additions to the listing of drugs either contraindicated with PAXLOVID or with other clinically significant drug interactions with PAXLOVID may be made in future EUA revisions; the drugs being added with this revision are listed below:

- Drugs being added to Section 4 (CONTRAINDICATIONS) and Table 1 in the Fact Sheet for HealthCare Providers; the list under “Do not take PAXLOVID if you are taking any of the following medicines” in the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers; and as medications with a red interaction code (contraindicated medications) in the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers:
    - Silodisin, eplerenone, ivabradine, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primodine, and lumacaftor/ivacaftor
- Drugs being added to Table 1 in the Fact Sheet for Healthcare Providers and as medications with a yellow interaction code (coadministration with PAXLOVID should be avoided and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary) in the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers:
    - Tamsulosin, rifapentine, aliskiren, ticagrelor, vorapaxar, clopidogrel, ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, everolimus, rimegepant, hydrocodone, oxycodone, suvorexant, tadalafil, avanafil, vardenafil, and sildenafil when used for erectile dysfunction (already included when used for pulmonary arterial hypertension).

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Section 7 (Drug Interactions) of the Fact Sheet for Healthcare Providers is also being revised for the following reasons:

- The text in Section 7.1 is being revised to emphasize that ritonavir is a strong CYP3A inhibitor. The text in Section 7.3 describing Table 1 is being revised to provide a suggestion for other resources that can be used to find comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor. Section 7.3 already included a statement that the drugs listed were a guide and not a comprehensive list of all possible drugs that may interact with PAXLOVID.
- Propoxyphene is being removed from Table 1 and from the list of contraindicated drugs in Section 4 (as well as from the list of contraindicated drugs in the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers) because it is no longer available in the United States.
- Bepridil is being removed from Table 1 because it is no longer available in the United States.
- For the anticonvulsants, the effect of PAXLOVID on the concentration of the anticonvulsants was removed as the reason for the contraindication is the effect of the anticonvulsants on the PAXLOVID concentration.
- The lists of anti-HIV protease inhibitors and other anti-HIV drugs are being streamlined to retain the commonly used antiretrovirals and to remove the antiretrovirals that are either no longer marketed or rarely prescribed in the United States. In addition, raltegravir is being removed for consistency with the raltegravir label, which lists other ritonavir-containing products (atazanavir/ritonavir, darunavir/ritonavir, and tipranavir/ritonavir) among the drugs without clinically significant interactions with raltegravir. Finally, the Effect on Concentration column for the Anti-HIV drug class was edited to include a concentration effect of PAXLOVID on nevirapine (↑ nevirapine), given nevirapine is extensively metabolized by CYP3A.
- The clinical comments related to the immunosuppressants (cyclosporine, tacrolimus, sirolimus, and now everolimus) in Table 1 are being revised to emphasize that use of PAXLOVID should be avoided when close monitoring of immunosuppressant concentrations is not feasible and to add language about monitoring for immunosuppressant-associated adverse reactions, immunosuppressant dose reduction, and obtaining expert consultation from the patient's immunosuppressive therapy specialist. The clinical comments already stated that therapeutic concentration monitoring is recommended, that PAXLOVID use should be avoided when close monitoring of immunosuppressant serum concentrations is not feasible, and to refer to the immunosuppressant product label for further administration if co-administered. However, given several post-authorization reports of hospitalizations for adverse reactions

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(including acute kidney injury) associated with elevated tacrolimus levels in patients who were co-administered tacrolimus and PAXLOVID without close monitoring of immunosuppressant serum concentrations, these revisions are being added for further clarity.

- The systemic corticosteroids drug class listing and clinical comment is being revised as some of the listed drugs are not available for systemic administration and to note that the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. In addition, prednisone is being removed from the listed corticosteroids with an established and other potentially significant drug interaction and instead being named as an alternative corticosteroid that can be considered for use with PAXLOVID for consistency with labels for other products that only contain 100 mg of ritonavir per dose.

Similar revisions are being made to the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers and the Patient Eligibility Screening Checklist Tool for Prescribers for consistency with the Fact Sheet for Healthcare Providers.

3. **To Update the Fact Sheet for Healthcare Providers with Information on Viral RNA Rebound in the Clinical Trial EPIC-HR**

   A "Viral RNA Rebound" subsection is being added to Section 12.4 of the PAXLOVID Fact Sheet for Healthcare Providers to communicate the results of analyses conducted both by the Sponsor and independently by FDA on rebounds in SARS-CoV-2 RNA levels in NP/nasal swab samples after treatment cessation in both PAXLOVID and placebo recipients in the pivotal clinical trial EPIC-HR. Anecdotal reports of viral RNA rebound with PAXLOVID use in the EUA setting have garnered attention in the media and in public forums; therefore, a summary of available data from the double-blinded, randomized, placebo-controlled trial EPIC-HR is provided to better inform healthcare providers about this issue. Please see the full separate clinical virology review by Patrick Harrington, Ph.D. for more details.

4. **To Revise the Patient Fact Sheet to Minimize Patient Medication Errors**

   The Fact Sheet for Patients, Parents, and Caregivers is being revised due to post-authorization reports of two types of medication errors. First, there have been a number of reports of PAXLOVID being prescribed to patients who are on concomitant medications that are contraindicated or not recommended for use with PAXLOVID. Consequently, the language in the "What should I tell my healthcare provider before I take PAXLOVID" section has been reorganized to emphasize the risk of serious side effects due to drug interactions with PAXLOVID. Second, there have been over 140 reports of a suspected wrong dose error. Of an analyzed subset, most occurred during patient administration

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and often involved patients taking the wrong tablets, and several patients said the patient fact sheet and instructions on the packaging were confusing. Consequently, the "How do I take PAXLOVID" section is being revised to include that there are 2 different dose packs (based on renal function), to emphasize that the tablets are taken together 2 times each day for 5 days, and to show a picture of the dose packs with instructions on where to find the morning and evening doses.

Summary of Fact Sheet Revisions:

- Section 1 of the Fact Sheet for Healthcare Providers (EMERGENCY USE AUTHORIZATION) was updated to reference the new CDC website for Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals, rather than the prior link which was intended for the general public (People with Certain Medical Conditions).

- Section 2.4 of the Fact Sheet for Healthcare Providers (Important Drug Interactions with PAXLOVID) was reordered and revised to include the following statement: "Interacting drugs listed in the Fact Sheet are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir."

- Section 4 of the Fact Sheet for Healthcare Providers (CONTRAINDICATIONS) was modified as follows:
    - The following statement was added: "Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir."
    - The following drugs were added to the list of drugs that are contraindicated due to being highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions: silodosin, eplerenone, ivabradine, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, voclosporin, flibanserin, and tolvaptan
    - The following drugs were added to the list of drugs that are contraindicated due to being potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance: primidone and lumacaftor/ivacaftor

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- Section 5.1 of the Fact Sheet for Healthcare Providers (Risk of Serious Adverse Reactions Due to Drug Interactions) was modified to add the following sentence: “Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.”

- Section 6.2 of the Fact Sheet for Healthcare Providers (Post-Authorization Experience) was modified to add the following adverse reactions identified during post-authorization use of PAXLOVID: abdominal pain, nausea, and malaise

- Section 7.1 of the Fact Sheet for Healthcare Providers (Potential for PAXLOVID to Affect Other Drugs) was minorly edited to emphasize that ritonavir is a strong CYP3A inhibitor.

- Section 7.3 of the Fact Sheet for Healthcare Providers (Established and Other Potentially Significant Drug Interactions) was modified as follows:
    - The text above the table was revised to provide a suggestion for other resources that can be used to find comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor.
    - Table 1 was revised to:
        - Add the following drugs: silodosin, eplerenone, ivabradine, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primidone, lumacaftor/ivacaftor, tamsulosin, rifapentine, aliskiren, ticagrelor, vorapaxar, clopidogrel, ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, everolimus, rimegepant, hydrocodone, oxycodone, suvorexant, tadalafil, avanafil, vardenafil, and sildenafil when used for erectile dysfunction (already included when used for pulmonary arterial hypertension).
        - Remove the following drugs: propoxyphene, bepridil, amprenavir, fosamprenavir, indinavir, nelfinavir, saquinavir, didanosine, delavirdine, raltegravir, and prednisone
        - Revise the clinical comments related to immunosuppressants and corticosteroids and make additional small edits.

- Section 12.4 of the Fact Sheet for Healthcare Providers (Microbiology) was revised to add a section on Viral RNA Rebound. This section reads as follows:

    Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients,

irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

- The Fact Sheet for Patients, Parents, and Caregivers was revised as follows:
  - The language in the "What should I tell my healthcare provider before I take PAXLOVID" section has been reorganized to emphasize the risk of serious side effects due to drug interactions with PAXLOVID.
  - The language in the "How do I take PAXLOVID" section was revised to include that there are 2 different dose packs (based on renal function), to emphasize that the tablets are taken together 2 times each day for 5 days and to show a picture of the dose packs with instructions on where to find the morning and evening doses.
  - The listing of medications under Do not take PAXLOVID if…you are taking any of the following medicines" was expanded to include the drugs being added to the list of contraindicated drugs and to reformat the list into several columns.
  - Abdominal pain, nausea, and feeling generally unwell were added to the possible side effects of PAXLOVID section.

A Dear Healthcare Provider Letter was also created to communicate the additions to the list of contraindicated drugs in the Fact Sheet for Healthcare Providers and to emphasize the need to assess for drug interactions.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID. The analysis of benefits and risks that underlies the authorization of EUA 105 remains unchanged.

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WENDY W CARTER
06/28/2022 11:03:52 AM

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW

EUA# 000105 **SDNs:** 118,130,131,136, 147, 154, 158, 159 **DATE REVIEWED:** 6/24/2022

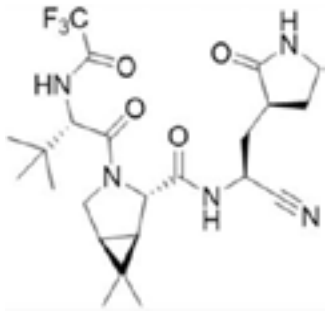
Reviewer: Patrick Harrington, PhD.

Assigned/Reviewed SDNs:

SDN	eCTD#	Rec'd Date	Assigned Date	Content
118	0115	4/26/2022	4/27/2022	Response to 4/22/22 request related to post-tx viral RNA rebound
130	0126	5/10/2022	5/10/2022	Response to 5/6/22 request for sponsor feedback on preliminary FDA analyses of viral RNA rebound
131	0127	5/11/2022	5/11/2022	Analysis of rebound in viral test results in "real world" database
136	0132	5/19/2022	5/20/2022	Response to 5/18/22 request regarding NP vs. nasal swab sampling
147	0143	6/6/2022	6/7/2022	Proposed revisions to HCP Fact Sheet
154	0149	6/16/2022	6/17/2022	Proposed revisions to HCP Fact Sheet
158	0153	6/23/2022	6/23/2022	Proposed revisions to HCP Fact Sheet
159	0154	6/24/2022	6/27/2022	Proposed revisions to HCP Fact Sheet

Sponsor: Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755
Karen Baker, Director, Pfizer Global Regulatory Affairs

Product Names: nirmatrelvir (PF-07321332, PAXLOVID™; coadministered with ritonavir)
Chemical Name: 1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide
Structure:



NIRMATRELVIR (PF-07321332)

Molecular Formula: $C_{23}H_{32}F_3N_5O_4$
Molecular Weight: 499.54 daltons
Drug Category: Antiviral
Indication: Treatment of mild-to-moderate COVID-19
Dosage Form/Route of administration: nirmatrelvir 150 mg tablet, co-administered with ritonavir (PK enhancer) 100 mg tablet / oral
Supporting documents: IND 153517
Abbreviations: 3CLpro, 3C-like protease; CoV, coronavirus; Mpro, main protease; NIR/r, nirmatrelvir/ritonavir; nsp, nonstructural protein; NP, nasopharyngeal; SARS, severe acute respiratory syndrome; VL(R), viral load (rebound)

1. BACKGROUND

Nirmatrelvir/ritonavir (NIR/r, PAXLOVID™, PF-07321332/r; EUA 000105 and IND 153517) received FDA Emergency Use Authorization on 12/22/2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

NIR is a reversible competitive inhibitor of the SARS-CoV-2 main protease (Mpro), also known as 3C-like protease (3CLpro) or nsp5 protease.

This set of submissions includes the sponsor's analyses and responses to DAV requests related to recent public reports of virologic and/or symptomatic "rebounds" following PAXLOVID treatment. In late April 2022, the Division became aware of case reports and stories in the press and social media related to patients who experienced symptomatic recovery during PAXLOVID treatment, but after stopping the 5-day course of treatment experienced "relapses" in COVID-19 symptoms which were coincident with rebounds in qualitative or quantitative viral RNA, antigen or virus detection in upper respiratory tract samples (e.g., see Gupta et al., 2022; Charness et al., 2022; Carlin et al., 2022; Washington Post 4/27/2022 article). These cases have occurred in immunocompetent, vaccinated individuals, indicating that the phenomenon is not attributed to immune deficiency. Furthermore, there has been no reported evidence that these cases are related to emergence of NIR-resistant virus. These reports have raised concerns and some speculation that PAXLOVID treatment may suppress virus replication in a manner that delays the development of a functional host immune response that is ultimately responsible for clearing the infection, and that a longer treatment duration or re-treatment of "relapse" cases may be needed for optimal efficacy and to minimize the risk of SARS-CoV-2 transmission from treated individuals.

This review summarizes post-hoc analyses conducted by the sponsor, and additional analyses independently conducted by FDA, to investigate the frequency, role of PAXLOVID treatment, and the potential clinical relevance of post-treatment SARS-CoV-2 RNA rebound using available virology, genotypic resistance and clinical data from the Phase 2/3 C4671005 (EPIC-HR) trial. The sponsor also investigated this topic using electronic health record data from PAXLOVID-prescribed patients. As described below, post-treatment viral RNA rebound could be observed in both treated and untreated infected populations and thus was not specifically linked to drug treatment.

Clinical trial C4671005 evaluated PAXLOVID safety and efficacy in non-hospitalized, unvaccinated, high-risk adult participants with mild-to-moderate COVID-19 and demonstrated a 5-day course of PAXLOVID treatment was associated with an ~88% reduction in the risk of COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo.

Nasopharyngeal (NP) swab samples, and in some cases nasal mid-turbinate swab samples (discussed below) for viral shedding and nucleotide sequencing analyses were collected at Baseline (Day 1), Day 3, Day 5 (End-of-Treatment), Day 10 and Day 14. Viral RNA levels were measured at a central laboratory ((b) (4)) using the Abbott RealTime Quantitative SARS-CoV-2 assay, which is a quantitative real-time RT-PCR assay. The assay targets the viral RNA-dependent RNA polymerase (nsp12) and nucleocapsid (N) genes. The assay has a lower limit of quantification (LLOQ) of 100 (2 $\log_{10}$) copies/mL. Note that based on previously reported data, ~99% of subjects enrolled in the trial with available viral sequencing data were infected with a SARS-CoV-2 Delta variant.

See the 12/22/2021 multidisciplinary review of EUA 000105, additional Clinical Virology analyses from the Original EUA 000105 submission package (EUA000105.000), and the subsequent Clinical Virology review of EUA 000105 SDNs 46-92 for detailed analyses of efficacy and resistance from this clinical trial C4671005.

2. SPONSOR'S ANALYSES OF VIRAL RNA REBOUND IN STUDY C4671005

Identification of Subjects with Post-treatment SARS-CoV-2 RNA Rebound

The sponsor's analyses of viral RNA rebound in clinical trial C4671005 (EPIC-HR) were summarized primarily in a slide deck submitted in SDN 118. Note that the terms "viral load (VL)" and "viral load rebound (VLR)" are included in some places below as this is the terminology used by the sponsor. However, we generally do not view viral RNA levels in NP or nasal swab samples as measures of "viral load." Viral RNA levels in these

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samples could be considered a measure of viral shedding in the upper respiratory tract, but they do not necessarily reflect virus or viral RNA levels in other anatomical compartments such as the lungs, nor should they be considered a measure of the overall body burden of virus or viral nucleic acid in a manner like blood plasma viral load in chronic infections like HIV or HCV.

Note that 95.3% of all viral RNA results reported in the full dataset from study C4671005 were derived from NP swab samples, while 4.5% were reported from "NOSTRIL" swab samples (remaining ~0.2% of results with unspecified sampling location). For analysis purposes all of these results were combined. The sponsor clarified in SDN 136 that Day 1 and Day 5 study visits were to occur in person and include NP swab sample collections, while some flexibility was allowed for Day 3, Day 10 and Day 14 visits. During an in-person visit, whether conducted in-clinic or by home health, an NP swab was to be collected by the healthcare provider. When visits were conducted by telemedicine, participants self-collected a nasal swab (i.e., "NOSTRIL" sampling site), which involved sampling both nostrils with the same swab up to ~2 cm into the nostrils until slight resistance is felt, consistent with a mid-turbinate swab (CDC 2022). Self-collected swabs were to be refrigerated until pickup by courier on the same day of collection, after which they were shipped to the central laboratory on dry ice. In many cases, sites chose to conduct an in-person visit even when telemedicine was an option, and as a result, NP collections also predominantly occurred at Day 3, Day 10 and Day 14. For Day 10 and Day 14 analysis visits, 90.3% and 92.1% of reported viral RNA results, respectively, were from NP swab samples. Note that viral RNA levels tend to be higher in NP samples compared to nasal mid-turbinate or other upper respiratory tract samples, and this was the case in the sponsor's dataset (analysis not shown), so inclusion of the Day 10 and Day 14 non-NP data in these analyses would not inflate the calculated rate of post-treatment viral RNA rebound.

The sponsor defined post-treatment "viral load rebound (VLR)" as follows:

- If Day14 viral RNA result is available:
  - Day 14 viral RNA change from Day 5 ≥0.5 Log_{10} copies/mL
  - Day 14 viral RNA ≥2.7 Log_{10} copies/mL
- If Day 14 viral RNA result is not available:
  - Day 10 viral RNA change from Day 5 ≥0.5 Log_{10} copies/mL
  - Day 10 viral RNA ≥2.7 Log_{10} copies/mL

Based on these criteria, the sponsor reported a viral RNA rebound rate of 2.1% (23/1106) for subjects who received PAXLOVID, and 1.5% (17/1110) for subjects who received placebo. Viral RNA kinetics for these individual subjects are shown in Figure 1 (Sponsor's 4/26/22 response document, pg. 18).

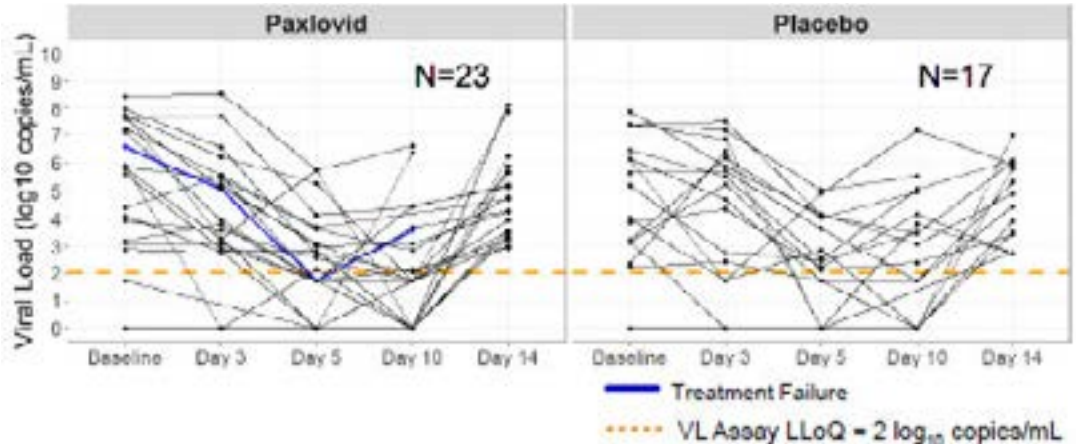

Figure 1. Viral RNA levels in NP/nasal swab samples for individual subjects identified by sponsor as having post-treatment viral RNA rebound in study C4671005 (EPIC-HR).

Note that this Day 14-focused criteria for viral RNA rebound would not capture earlier, transient rebounds in viral RNA levels that were observed on Day 10 but not on Day 14. Also, the definition would not capture rebounds in viral RNA levels from Day 5 <LLOQ (<2 $\log_{10}$ copies/mL) if the RNA level at the assessed post-treatment timepoint was >LLOQ but <2.7 $\log_{10}$ copies/mL. Also note that the sponsor calculated the "rates" of viral RNA rebound using all enrolled and treated subjects as denominators, not just those with viral RNA results available on Day 5 and Day 10 or Day 14.

The sponsor commented further in SDN 130 that the RT-PCR assay is likely too sensitive to detect clinically relevant "viral load rebound" as it is highly likely that it is detecting residual viral RNA fragments from the infection itself, which the sponsor will investigate further in cell culture infectivity analyses. As further justification for the sponsor's analysis parameters, the sponsor's analyses were aligned with the lower limit of viral RNA for sequencing analyses and were focused on investigating the relationship between viral RNA rebound and NIR resistance. The sponsor also commented that infections that had resolved by Day 14 (i.e., those with earlier transient rebounds no longer detected at Day 14) were not considered as clinically meaningful or biologically critical for investigating the role of NIR resistance.

Additional analysis parameters for identification of post-treatment viral RNA rebound were investigated in independent FDA analyses, which are described later in this review. While most of the independent FDA analyses focused on a more sensitive definition of post-treatment viral RNA rebound, in this reviewer's opinion the clinical relevance of viral RNA rebound identified by any criteria is unclear, and thus there is no single established "ideal" set of criteria for identifying patients with post-treatment viral RNA rebound.

Investigations into Relationship between Viral RNA Rebound, Drug Exposures, Clinical Outcomes, and Nirmatrelvir Resistance

The sponsor conducted an exploratory analysis to determine if viral RNA rebound was associated with reduced NIR exposure. In subjects with viral RNA rebound (sponsor-defined), NIR exposures generally did not differ from the overall PAXLOVID treatment population (Figure 2; Sponsor's 4/26/22 response document, pg. 19).

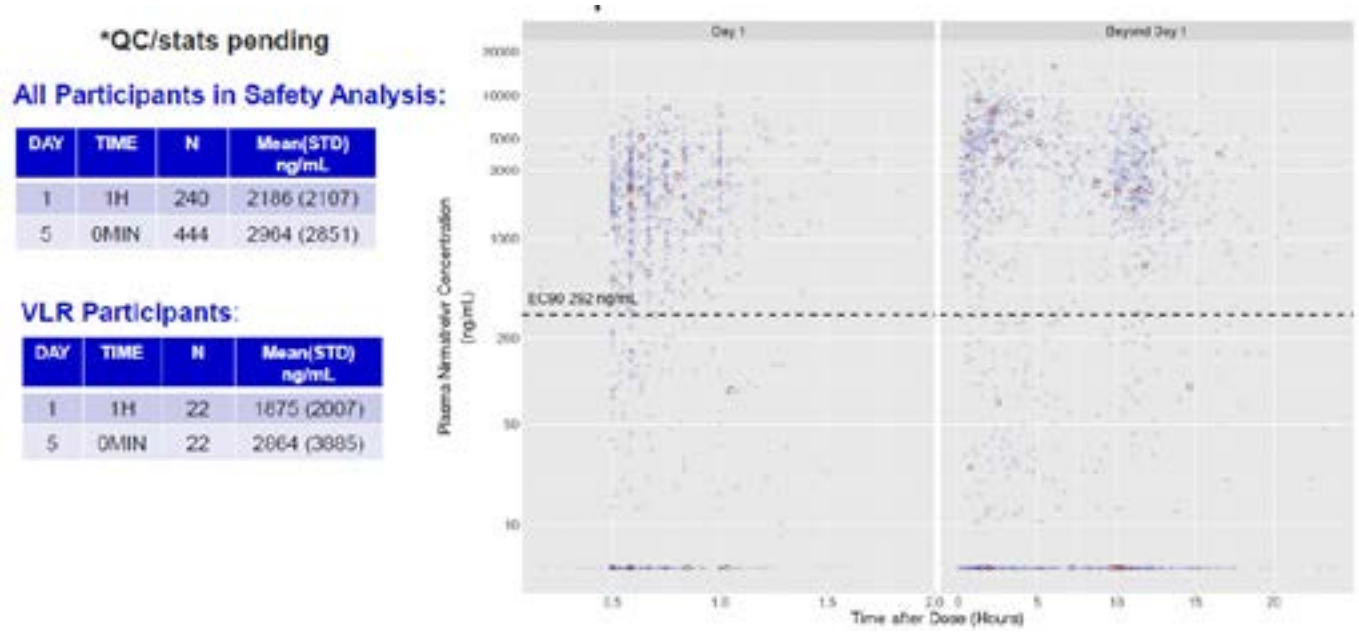

Figure 2. Nirmatrelvir plasma exposures in PAXLOVID-treated subjects with and without post-treatment viral RNA rebound (sponsor-defined) in study C4671005. In the charts presumably the red circles indicate subjects with viral RNA rebound. The noted nirmatrelvir EC_{90} value (292 ng/mL, 585 nM) refers to the unbound EC_{90} value against SARS-CoV-2 in differentiated normal human bronchial epithelial (dNHBE) cells.

Post-treatment viral RNA rebound was not associated with recurrence of moderate-severe symptoms (Figure 3; Sponsor's 4/26/22 response document, pg. 21). Only one PAXLOVID treated subject ((b) (6)) had moderate-severe symptoms temporally associated with viral RNA rebound, while 17 other PAXLOVID treated subjects (including hospitalized subject (b) (6)) had moderate-severe symptoms that were not temporally associated but rather preceded and in most cases had resolved by the time of viral RNA rebound. Note that these analyses did not consider mild symptoms.

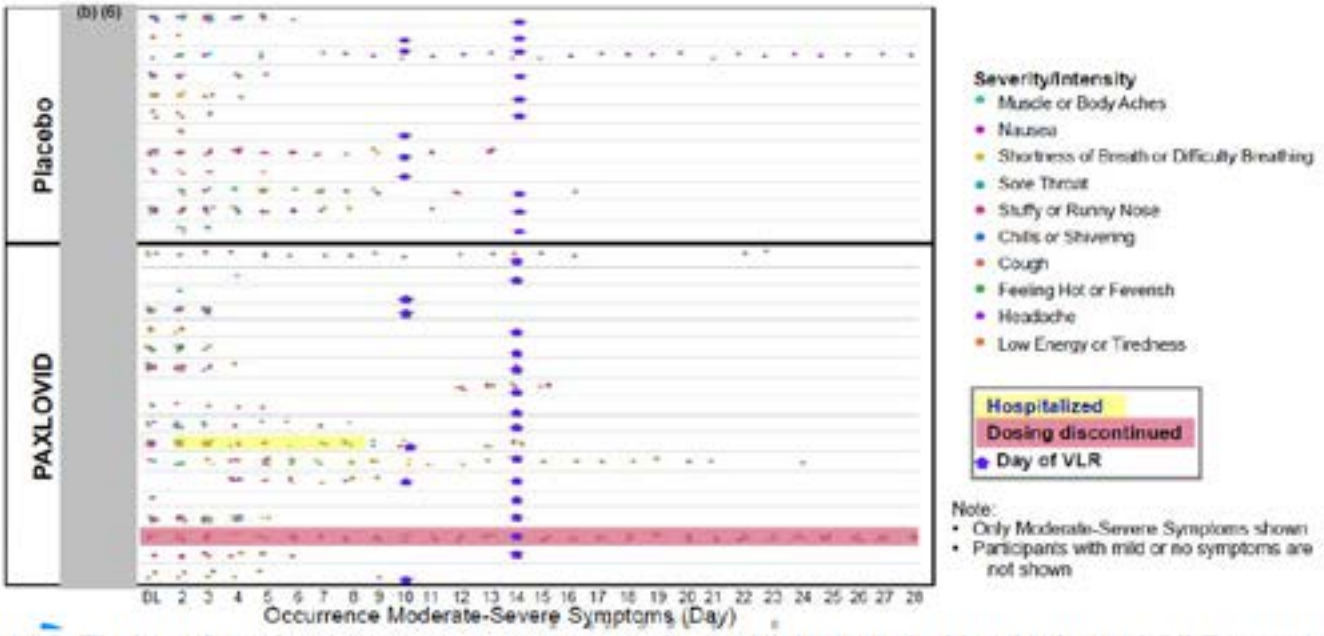

Figure 3. Timing of moderate-severe symptoms and post-treatment viral load rebound (VLR, sponsor-defined) in study C4671005 (EPIC-HR).

The primary clinical endpoint of hospitalization/death was not associated with post-treatment viral RNA rebound (Figure 4; Sponsor's 4/26/22 response document, pg. 22). Only 1 PAXLOVID treated subject ((b) (6)) who was hospitalized met the sponsor's definition of post-treatment viral RNA rebound, and hospitalization first occurred on Day ~2, preceding the timing of viral RNA rebound. Subject (b) (6) did not meet the sponsor's definition of viral RNA rebound but did show an increase in viral RNA level from Day 10 to Day 14; the subject was hospitalized on Day ~8, again preceding the timing of viral RNA rebound.

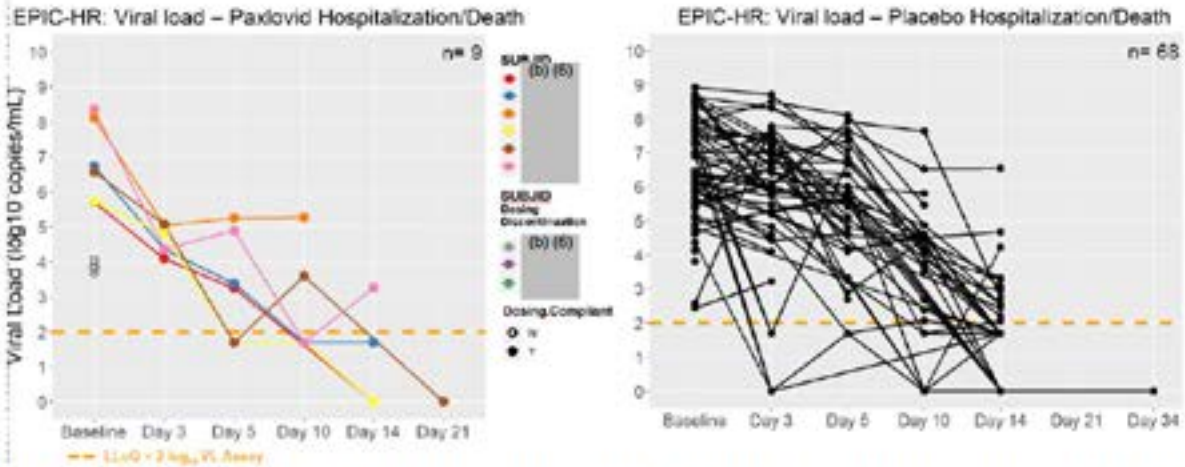

Figure 4. Viral RNA levels in NP/nasal swab samples in subjects who experienced hospitalization or death in study C4671005 (EPIC-HR).

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The sponsor also reported that viral RNA rebound was not associated with the emergence of amino acid substitutions in SARS-CoV-2 Mpro or Mpro cleavage sites (Figure 5; Sponsor's 4/26/22 response document, pg. 26). Among subjects with sponsor-defined post-treatment viral RNA rebound and with available viral sequence analysis data, any Mpro or Mpro cleavage site treatment-emergent amino acid substitution was detected in 33% (6/18) of PAXLOVID treated subjects and 31% (4/13) of placebo treated subjects. No treatment-emergent substitutions were detected at a NIR contact residue or other known or potentially important resistance-associated position in Mpro. The sponsor noted additional viral infectivity and phenotypic analyses are ongoing.

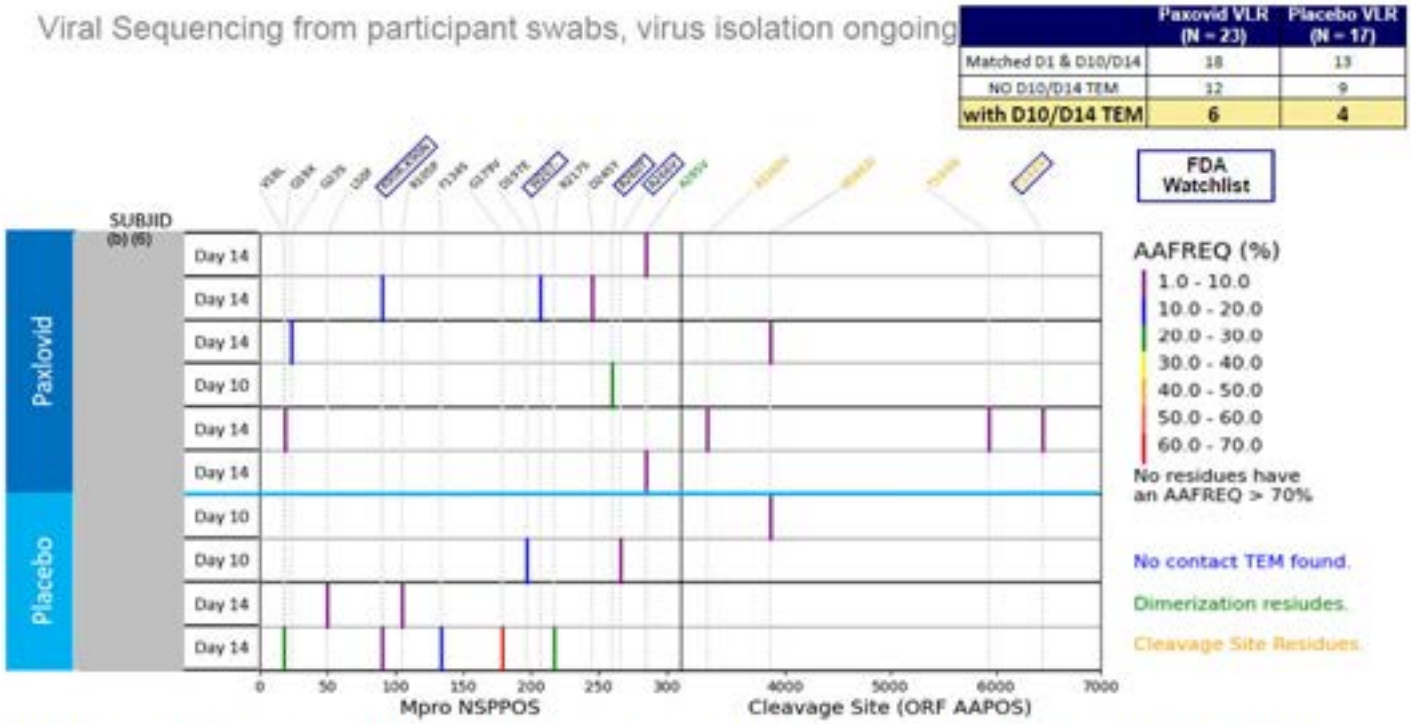

Figure 5. Treatment-emergent amino acid substitutions (5% frequency cutoff) detected in SARS-CoV-2 Mpro or Mpro cleavage sites in NP/nasal swab samples from subjects with sponsor-defined post-treatment viral RNA rebound in study C4671005 (EPIC-HR). "Treatment-emergent mutation (TEM)" refers to any treatment-emergent amino acid substitution in Mpro or an Mpro cleavage site.

The sponsor also reviewed concomitant medications and concluded that there were no particular patterns of concomitant medications that appear to have direct or indirect implications for post-treatment viral RNA rebound.

In summary, in the sponsor's analyses of clinical trial C4671005, post-treatment viral RNA rebound was observed in a subset of PAXLOVID and placebo treated subjects, and the sponsor found no association between post-treatment viral RNA rebound and hospitalization or death, moderate symptoms, drug resistance, nirmatrelvir exposures, or concomitant medications.

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3. INDEPENDENT FDA ANALYSES OF VIRAL RNA REBOUND IN STUDY 4671005

Identification of Subjects with Post-treatment SARS-CoV-2 RNA Rebound

Viral RNA data reported from Study 4671005 were independently analyzed to characterize the frequency and potential clinical relevance of rebounds in viral RNA levels following treatment with PAXLOVID or placebo. These analyses used the ADMC dataset reported in SDN 65.

As previously documented (EUA000105.000; EUA 000105 SDNs 46-92), treatment with PAXLOVID was, on average, associated with a consistent and more rapid decline in viral RNA levels compared to placebo, with a ~0.8 $\log_{10}$ copies/mL greater mean decline in viral RNA levels through Day 5/end-of-treatment (Figure 6-top, FDA analysis). However, it should be noted that there was substantial inter- and intra-subject variability in viral RNA levels over time, with evidence of fluctuations in viral RNA levels for individual subjects throughout the study period (Figure 6-bottom, FDA analysis).

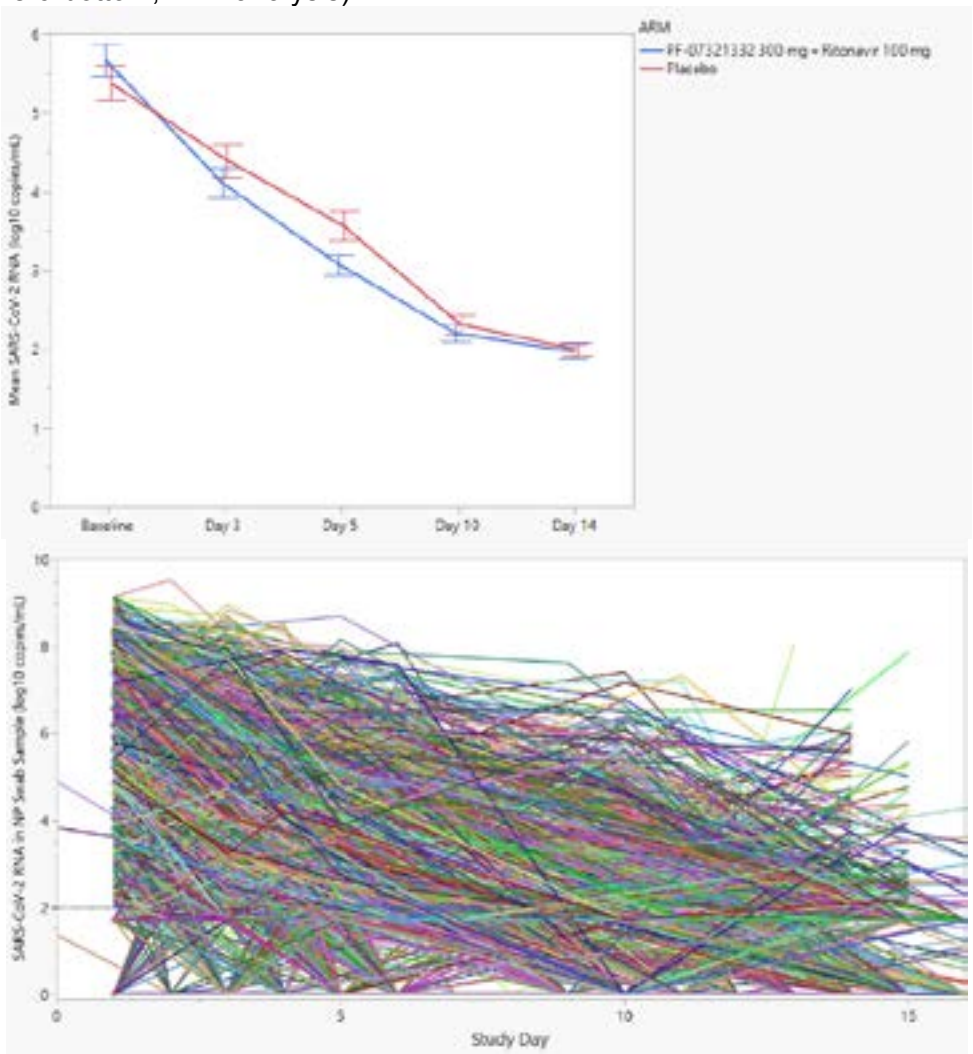

Figure 6. Mean SARS-Cov-2 RNA levels within each analysis visit window for PAXLOVID (i.e., PF—07321332 + ritonavir) and placebo treated subjects (top), and results by specific Study Day for individual subjects (bottom). Dashed horizontal line indicates assay LLOQ (2 $\log_{10}$ copies/mL).

The following definitions of viral RNA rebound were considered for identification of post-treatment rebound:

Day 10 (LLOQ): Day 5 <LLOQ, Day 10 ≥LLOQ
Day 10 (LLOQ-2.5): Day 5 <LLOQ, Day 10 ≥2.5 (LLOQ + 0.5 $\log_{10}$)
Day 10 (0.5): Day 5 ≥LLOQ, Day 10 ≥0.5 $\log_{10}$ copies/mL increase from Day 5
Day 10 (LLOQ/0.5 Combined): Day 10 (LLOQ) PLUS Day 10 (0.5)
Day 10 (LLOQ-2.5/0.5 Combined): Day 10 (LLOQ-2.5) PLUS Day 10 (0.5)
Day 14 (LLOQ): Day 5 <LLOQ, Day 14 ≥LLOQ
Day 14 (LLOQ-2.5): Day 5 <LLOQ, Day 14 ≥2.5 (LLOQ + 0.5 $\log_{10}$)
Day 14 (0.5): Day 5 ≥LLOQ, Day 14 ≥0.5 $\log_{10}$ copies/mL increase from Day 5
Day 14 (LLOQ/0.5 Combined): Day 14 (LLOQ) PLUS Day 14 (0.5)
Day 14 (LLOQ-2.5/0.5 Combined): Day 14 (LLOQ-2.5) PLUS Day 14 (0.5)
Day 10/14 (LLOQ): Day 5 <LLOQ, Day 10 OR Day 14 ≥LLOQ
Day 10/14 (LLOQ-2.5): Day 5 <LLOQ, Day 10 OR Day 14 ≥2.5 (LLOQ + 0.5 $\log_{10}$)
Day 10/14 (0.5): Day 5 ≥LLOQ, Day 10 OR Day 14 ≥0.5 $\log_{10}$ copies/mL increase from Day 5
Day 10/14 (LLOQ/0.5 Combined)*: Day 10/14 (LLOQ) PLUS Day 10/14 (0.5)
Day 10/14 (LLOQ-2.5/0.5 Combined): Day 10/14 (LLOQ-2.5) PLUS Day 10/14 (0.5)
**Most sensitive analysis of post-treatment viral RNA rebound: Any evidence of viral RNA rebound from Day 5 to Day 10 or 14, based on <LLOQ to ≥LLOQ, or 0.5 $\log_{10}$ copies/mL increase from Day 5.*

In these analyses all denominators were based on the numbers of subjects with data at the timepoint(s) under consideration. The purpose of the LLOQ-2.5 analyses (i.e., <LLOQ on Day 5, followed by increase to 0.5 $\log_{10}$ above LLOQ on Day 10 or Day 14) was to account for possible assay variability around the assay LLOQ value (2.0 $\log_{10}$ copies/mL). While the data were analyzed with all of these definitions to assess the impact of different definitions on the estimated rate of viral RNA rebound, most subsequent analyses used the "Day 10/14 (LLOQ/0.5 Combined)" definition, which identified subjects with any evidence of viral RNA rebound from Day 5 (End-of-Treatment) to Day 10 or 14, based on RNA levels <LLOQ at Day 5 to ≥LLOQ on either Day 10 or Day 14, or, a 0.5 $\log_{10}$ copies/mL increase from Day 5 level on either Day 10 or Day 14.

The calculated rates of post-treatment viral RNA rebound are summarized in Table 1 and Figure 7 (FDA analyses). Based on the most sensitive Day 10/14 (LLOQ/0.5 Combined) definition, post-treatment viral RNA rebound could be observed in 8.1% (80/1106) of PAXLOVID recipients and 5.4% (53/1110) of placebo recipients.

We also analyzed the same viral RNA dataset using the sponsor's definition of "viral load rebound" and confirmed the sponsor's reported rate of rebound: 2.1% (23/1106) for PAXLOVID recipients and 1.5% (17/1110) for placebo recipients (2.3% and 1.7%, respectively, with denominators based on subjects with available viral RNA data at Day 5 and Day 10 or 14). Thus, the FDA Day 10/14 (LLOQ/0.5 Combined) definition identified approximately 3- to 4-fold more cases of post-treatment viral RNA rebound compared to the sponsor's definition.

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Table 1. Proportions of subjects with post-treatment viral RNA rebound according to analysis definition.

	PAXLOVID (N=1106)	Placebo (N=1110)
Day 10		
N	929	914
Day 10 (LLOQ)	26 (2.8%)	13 (1.4%)
Day 10 (LLOQ-2.5)	20 (2.2%)	7 (0.8%)
Day 10 (0.5)	32 (3.4%)	27 (3.0%)
Day 10 (LLOQ/0.5 Combined)	58 (6.2%)	40 (4.4%)
Day 10 (LLOQ-2.5/0.5 Combined)	52 (5.6%)	34 (3.7%)
Day 14		
N	948	950
Day 14 (LLOQ)	14 (1.5%)	9 (0.9%)
Day 14 (LLOQ-2.5)	10 (1.1%)	6 (0.6%)
Day 14 (0.5)	11 (1.2%)	8 (0.8%)
Day 14 (LLOQ/0.5 Combined)	25 (2.6%)	17 (1.8%)
Day 14 (LLOQ-2.5/0.5 Combined)	21 (2.2%)	14 (1.5%)
Day 10 OR Day 14		
N	990	980
Day 10/14 (LLOQ)	37 (3.7%)	21 (2.1%)
Day 10/14 (LLOQ-2.5)	28 (2.8%)	12 (1.2%)
Day 10/14 (0.5)	43 (4.3%)	32 (3.3%)
Day 10/14 (LLOQ/0.5 Combined)	80 (8.1%)*	53 (5.4%)*
Day 10/14 (LLOQ-2.5/0.5 Combined)	71 (7.2%)*	44 (4.5%)*

*p<0.05 Fisher's Exact Test PAXLOVID vs. Placebo
(note: did not test other data)

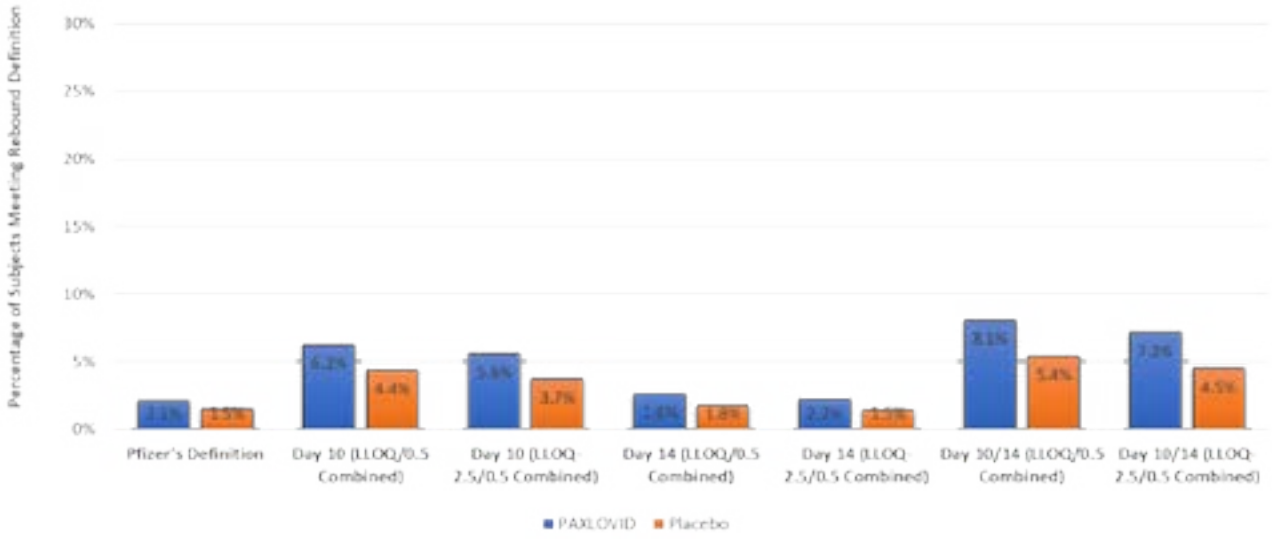

Figure 7. Proportions of subjects with post-treatment viral RNA rebound according to different analysis definitions.

Despite the overall similar rates of viral RNA rebound in the PAXLOVID and placebo groups across different definitions, the results based on the FDA Day 10/14 (LLOQ/0.5 Combined) analysis definition were significantly

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different between PAXLOVID and placebo recipients (8.1% versus 5.4%, respectively, p=0.02, Fisher's Exact test). Note that post-treatment viral RNA rebound definitions generally would not capture subjects with a slow or inapparent viral RNA decline through Day 5. Not surprisingly, nearly all subjects (94% across both arms [120/127, excl. 6 subjects w/o baseline result]) who met the FDA Day 10/14 (LLOQ/0.5 Combined) definition of post-treatment viral RNA rebound had a ≥1 $\log_{10}$ copies/mL decline in viral RNA level from baseline to Day 5, or otherwise a Day 5 viral RNA level <LLOQ.

Table 2 (FDA analysis) summarizes the Day 5 virologic responses observed in the PAXLOVID and placebo groups. Consistent with previous analyses, subjects who received PAXLOVID were more likely to show a decline in viral RNA levels from baseline to Day 5. Therefore, it is possible that the higher proportion of PAXLOVID-treated subjects achieving a virologic response on Day 5 could contribute to a higher post-treatment (i.e., post-Day 5) viral RNA rebound rate. The sponsor also investigated and discussed this potential confounding factor in SDN 130.

Table 2. Proportions of subjects with a viral RNA response from baseline to Day 5 (or Day 5 <LLOQ).

	PAXLOVID	Placebo
N	979	980
Day 5 RNA decline from baseline (median $\log_{10}$ copies/mL)	2.19	1.34
Day 5 >=1 log decline	644 (65.8%)	547 (55.8%)
Day 5 >=1 log decline OR <LLOQ	896 (91.5%)	816 (83.3%)
Day 5 >= 2 log decline	519 (53.0%)	385 (39.3%)
Day 5 >=2 log decline or <LLOQ	827 (84.5%)	698 (71.2%)

Note: Considering subjects who had paired Baseline/Day 5 data

To address the confounding factor of different on-treatment virologic response rates, an additional analysis of post-treatment viral RNA rebound was conducted focusing on the subgroup of subjects who could be classified as virologic responders on Day 5. As shown in Table 3 (FDA analysis), when the analysis was restricted to Day 5 virologic responders, the post-treatment viral RNA rebound rates among PAXLOVID and placebo recipients narrowed and were no longer significantly different. In other words, among those who had a decline in viral RNA level from baseline to Day 5, or a Day 5 viral RNA <LLOQ, there was not a clear difference in the likelihood of viral RNA rebound after Day 5 between those who had received PAXLOVID versus those who received placebo. These results indicate that the greater Day 5 response rate in PAXLOVID recipients likely contributed to some of the difference in the calculated rebound rates between the overall PAXLOVID and placebo groups.

Table 3. Post-treatment viral RNA rebound rates (LLOQ/0.5 Combined definition) according to Day 5 virologic responses.

	PAXLOVID	Placebo	P Value[2]
All subjects (with Day 5 and Day 10/14 viral RNA data)	8.1% (80/990)	5.4% (53/980)	0.020
All subjects in Day 5 virologic response analysis[1]	7.7% (74/967)	5.5% (53/959)	0.066
Day 5 ≥1 $\log_{10}$ copies/mL decline from baseline, OR <LLOQ[1]	7.9% (70/884)	6.3% (50/798)	0.218
Day 5 ≥2 $\log_{10}$ copies/mL decline from baseline, OR <LLOQ[1]	7.5% (61/815)	6.1% (42/685)	0.308

[1]Considering subjects who had paired Baseline/Day 5 data, plus either Day 10 or Day 14 data to assess post-treatment rebound
[2]Fisher's Exact Test

As further evidence that PAXLOVID treatment, regardless of any post-treatment viral RNA rebound, did not ultimately result in delayed clearance in viral RNA shedding, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ at all analysis visits (Table 4, FDA analysis). Based on these results, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely detected from a PAXLOVID treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 4. Proportions of subjects with viral RNA <LLOQ at each analysis visit.

	PAXLOVID	Placebo
Day 3	35.5% (369/1038)	34.1% (355/1040)
Day 5	47.4% (475/1002)	43.9% (439/1001)
Day 10	77.4% (765/989)	70.3% (676/962)
Day 14	89.1% (899/1009)	86.4% (869/1006)

Viral RNA levels for individual subjects identified as having post-treatment viral RNA rebound according to the sponsor's or FDA Day 10/14 (LLOQ/0.5 Combined) definitions are illustrated in Figure 8 (FDA analysis). Most of the differences in the calculated rates of viral RNA rebound between the sponsor's and FDA Day 10/14 (LLOQ/0.5 Combined) definitions are explained by subjects with transient viral RNA rebounds on Day 10 that were not observed on Day 14, which would not have been captured in the sponsor's definition. Of note, viral RNA rebound was detected more frequently on Day 10 relative to Day 14 in both the PAXLOVID and placebo groups.

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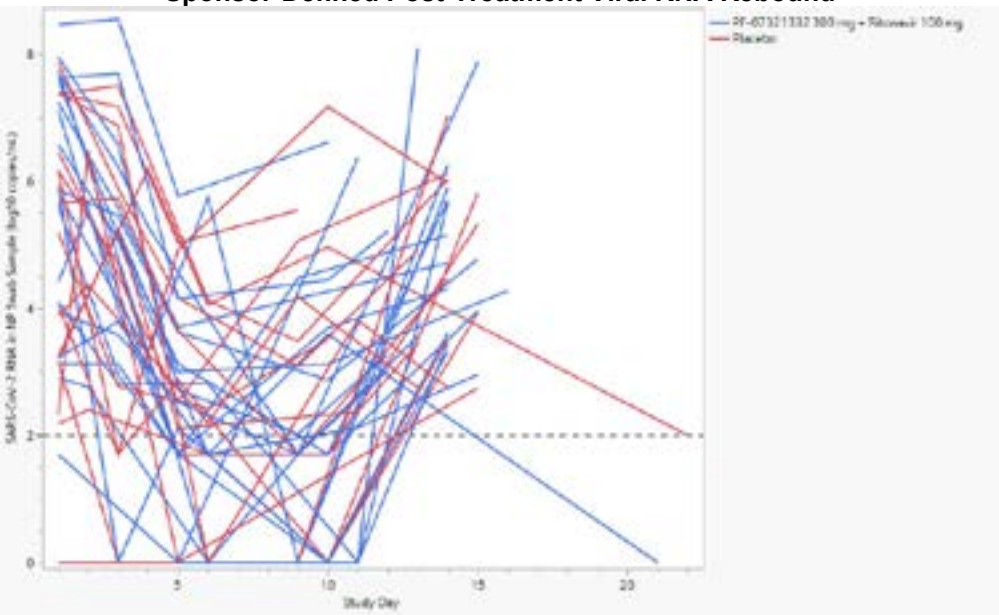
Sponsor-Defined Post-Treatment Viral RNA Rebound



FDA-Defined Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined])

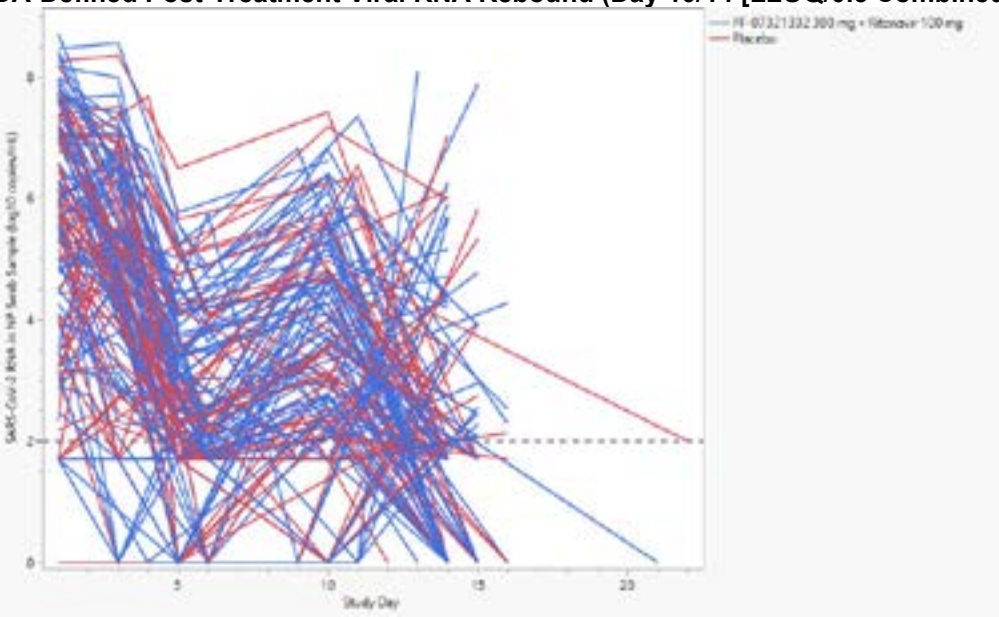


Figure 8. Viral RNA levels for individual subjects with post-treatment viral RNA rebound. Dashed horizontal line indicates assay LLOQ (2 $\log_{10}$ copies/mL).

Investigations into Relationship between Viral RNA Rebound, Clinical Outcomes, and Nirmatrelvir Resistance

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28. Among the 133 subjects in the PAXLOVID and placebo arms who experienced post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition), only 4 subjects (3%) reached the hospitalization or death endpoint (0 deaths), including 1 PAXLOVID recipient and 3 placebo recipients. Viral RNA results from these subjects are shown in Figure 9 (FDA analysis) and indicate there was not a consistent temporal relationship between post-Day 5 viral RNA rebound and the timing of hospitalization in these subjects. The hospitalization in the PAXLOVID recipient

(Subject (b) (6)) occurred early during treatment and the subject was discharged from the hospital on Day 8 prior to the post-treatment viral RNA rebound on Day 10, and the subject was not re-admitted to the hospital. One placebo treated subject (Subject (b) (6)) was admitted to the hospital on Day 9 around the time of viral RNA rebound observed on Day 10, but clearly this could not be attributed to a "post-treatment" viral RNA rebound and rather reflects some of the natural variability in COVID-19 disease progression.

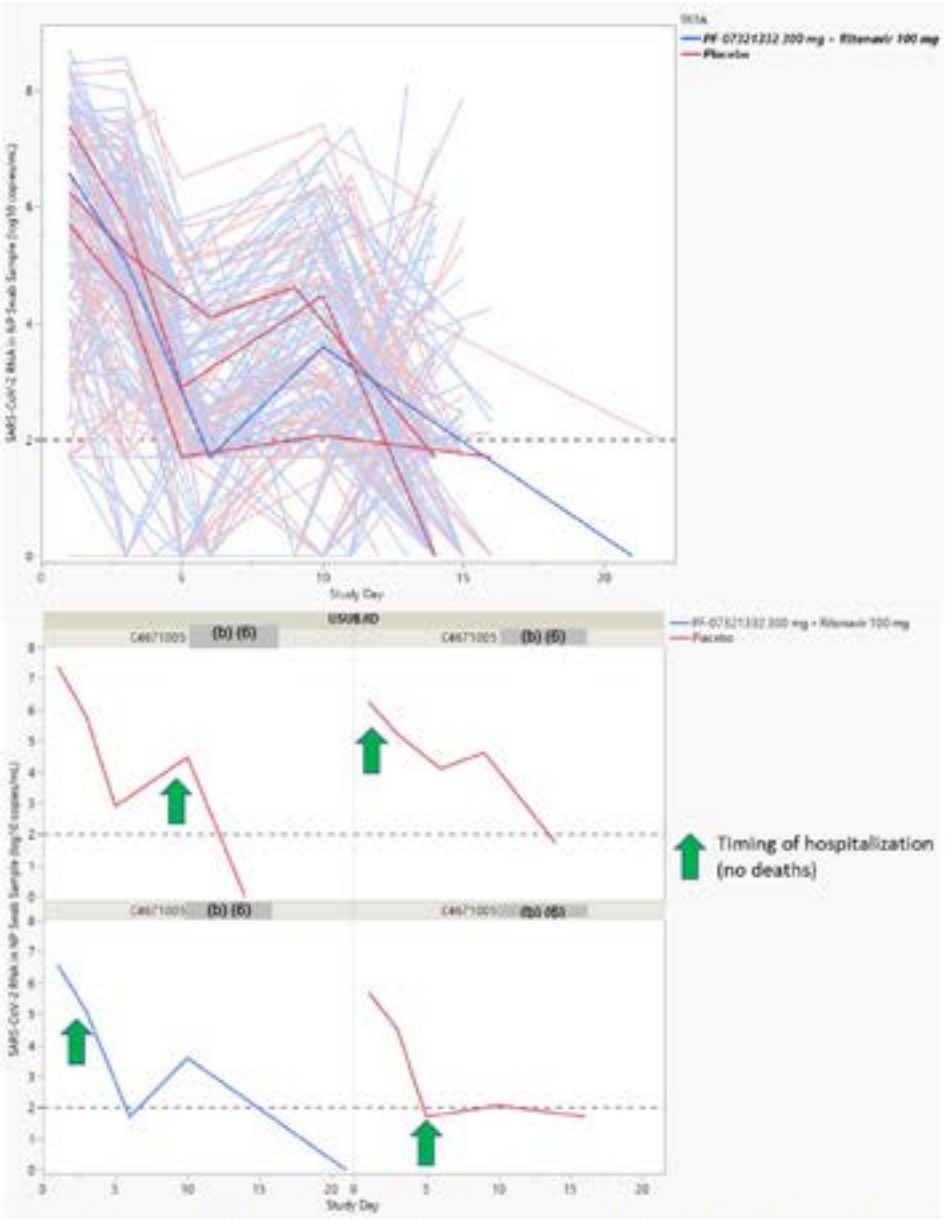


Figure 9. Viral RNA levels in subjects who experienced post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition) and reached the primary clinical endpoint of COVID-19-related hospitalization or death from any cause through Day 28. The top panel shows the 4 subjects with viral RNA rebound and COVID-19-related hospitalization (no deaths) in the foreground, with all other subjects with viral RNA rebound in the background. The bottom panels show the results for each of the 4 subjects relative to the timing of hospitalization. Dashed horizontal line indicates assay LLOQ (2 $\log_{10}$ copies/mL).

Post-treatment viral RNA rebound was not associated with baseline immunosuppression or HIV-1 infection, although this was a small subgroup of subjects in the trial (n=6 PAXLOVID, n=8 placebo). Viral RNA results for

the 14 subjects with baseline immunosuppression or HIV-1 infection are shown in Figure 10 (FDA analysis). Only one of these subjects experienced post-treatment viral RNA rebound, and the subject received placebo. None of the subjects experienced the clinical endpoint of hospitalization or death.

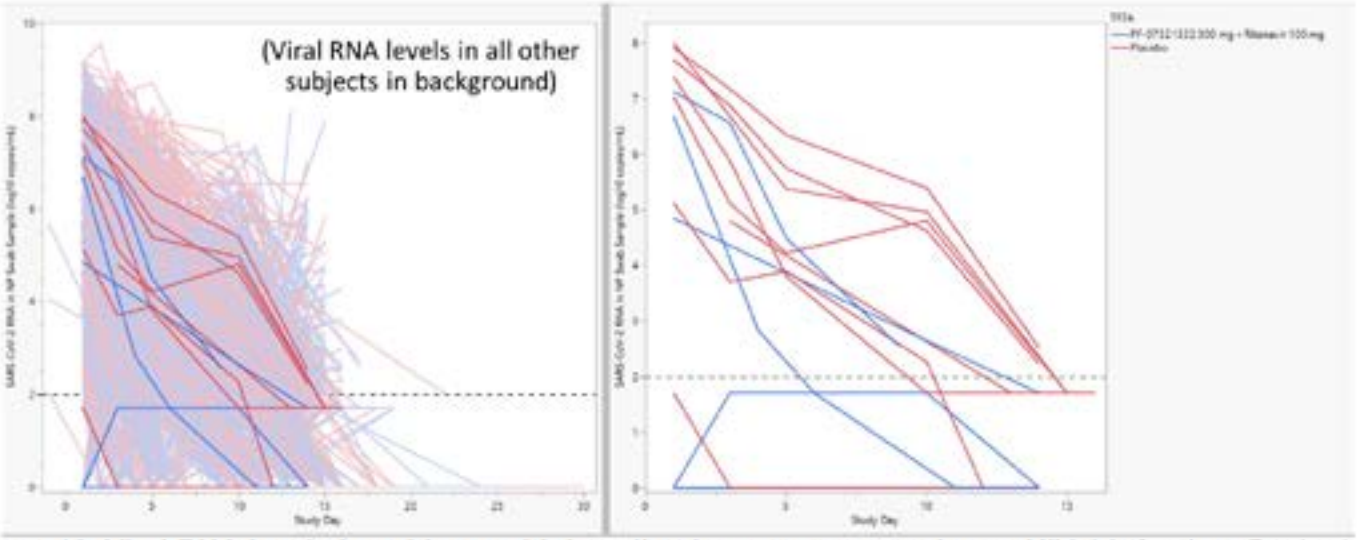


Figure 10. Viral RNA levels in subjects with baseline immunosuppression or HIV-1 infection. Dashed horizontal line indicates assay LLOQ (2 $\log_{10}$ copies/mL).

Consistent with the sponsor's analyses, we did not find an association between post-treatment viral RNA rebound and evidence of NIR resistance based on viral sequencing data. As shown in Table 5 (FDA analysis), among subjects who experienced post-treatment viral RNA rebound, the detection of treatment-emergent, potential NIR resistance-associated substitutions was no more common among PAXLOVID recipients relative to placebo recipients. For these analyses, a 5% sensitivity cutoff was used to detect amino acid substitutions, and we focused on identifying treatment-emergent substitutions at Mpro amino acid positions that could be involved in NIR susceptibility and resistance based one or more of the following criteria: (1) position in or near the NIR binding site (within ~5 angstroms), (2) position where substitution(s) have been shown to confer reduced phenotypic susceptibility to NIR, or (3) position where amino acid substitutions emerged in mouse hepatitis virus (MHV, surrogate coronavirus) selected for resistance to NIR. Two of these amino acid positions (186 and 189) were suspected of having a high degree of sequencing artifacts in previous resistance analyses from C4671005; therefore, analyses were conducted both including and excluding these positions. Note that viral sequencing data from the trial were not fully complete at the time of these analyses, so additional analyses will be conducted as more data become available.

Table 5. Proportions of subjects with post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition) who had treatment-emergent amino acid substitutions detected at a potential nirmatrelvir resistance-associated position in Mpro.

	PAXLOVID	Placebo
All Mpro Positions of Interest[1]	43% (18/42)	44% (12/27)
All Mpro Positions of Interest, excluding 186/189[2]	7% (3/42)	15% (4/27)

[1]Positions near NIR binding site, where AA substitutions confer reduced phenotypic susceptibility, or where AA substitutions emerged in drug-selected MHV (15, 41, 49, 50, 54, 55, 126, 129, 135, 140, 141, 142, 143, 144, 145, 163, 164, 165, 166, 167, 168, 172, 186, 187, 188, 189, 190, 191, 192, 248)
[2]Positions 186 and 189 have a high frequency of changes suspected due to sequencing artifacts

Viral RNA levels for each of the 7 subjects with a treatment-emergent, potential NIR resistance-associated substitution (excluding positions 186/189) are shown in Figure 11 (FDA analysis). Given that a comparable number of PAXLOVID and placebo recipients had one of these emergent amino acid substitutions detected, their emergence cannot clearly be attributed to PAXLOVID drug pressure and drug resistance. Nevertheless, the one PAXLOVID treated subject with treatment-emergent Mpro E166V (detected at a ~8% frequency) is noted as this has been flagged previously as being a potentially important resistance-associated substitution. Overall in C4671005, treatment-emergent E166V was detected in 3 PAXLOVID treated subjects and 0 placebo treated subjects, and in a biochemical assay an E166A substitution conferred a 33-fold reduction in NIR susceptibility. More recently, a preprint publication by Zhou et al., 2022 reported E166V engineered into SARS-CoV-2 conferred 25-fold and 267-fold increases in nirmatrelvir EC_{50} values in two different cell lines. Therefore, it is possible that in this one subject, post-treatment viral RNA rebound was associated with the emergence of a NIR resistance-associated substitution, but it is challenging to draw a firm conclusion given the single subject observation with a low frequency of detection, as well as the emergence of other potential NIR resistance-associated substitutions among placebo recipients.

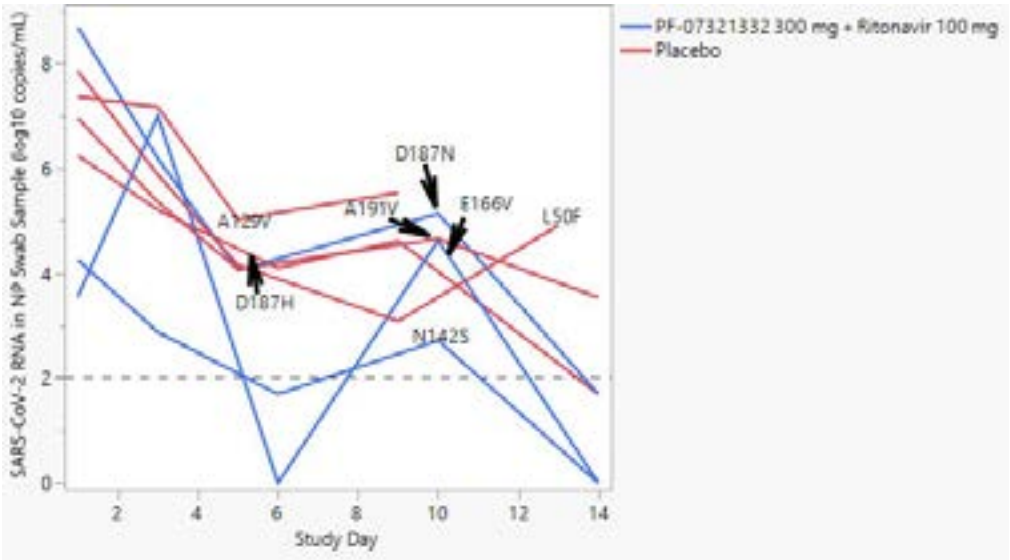


Figure 11. Viral RNA levels for individual subjects with treatment-emergent, potential nirmatrelvir resistance-associated amino acid substitutions detected in Mpro (excluding changes at positions 186/189). Dashed horizontal line indicates assay LLOQ (2 log_{10} copies/mL).

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4. VIRAL TESTING REBOUND IN "REAL WORLD" DATABASE

The Sponsor investigated the feasibility of using real-time electronic health record data to identify PAXLOVID-prescribed patients who tested positive for COVID-19 after a negative test for COVID-19 using the Truveta U.S. Health Systems database. According to the sponsor, Truveta partners with 20 health systems, and data from 7 health systems contributed to this analysis. Truveta de-identifies billions of clinical data points and aggregates them daily in the Truveta Platform.

The research questions investigated included the following:

1. How often is testing for COVID-19 performed following a PAXLOVID prescription?
2. What are the COVID-19 testing result patterns following a PAXLOVID prescription?
3. How often does a patient who received PAXLOVID test negative for COVID-19 and later test positive?

There are several limitations to these analyses. The sponsor noted that data quality evaluation for this analysis is for feasibility studies only, and the reported data have not undergone full validation. Manual chart review to confirm accuracy was not performed and data quality assessments were performed ad hoc while authoring data extraction queries. Also, normalization of test result values/terminology is ongoing. The platform also captures medication orders and does not confirm patients filled the medication or took the medication as prescribed.

Also note that these analyses were focused on RT-PCR laboratory tests for SARS-CoV-2 that were administered by the member health system. There is no description about the actual site sampled for the RT-PCR assay. Also, laboratory tests administered outside the health system, including community-operated laboratories and at-home tests, may not be reconciled to the patient's medical record. Thus, patients who were tested outside the health system and did not have a healthcare contact that would result in a laboratory test reconciliation would be missing from this analysis. Home tests (e.g. rapid home antigen testing) are not included in these data.

Of the 46,389,076 patients identified in the Truveta Platform from 12/23/2021 to 5/6/2022, 6,281 patients were identified as receiving a prescription order for PAXLOVID. Of those 6,281 patients, only 49 received a test for COVID-19 within 6-27 days following their PAXLOVID prescription. Of the 49 patients tested, 26 patients tested positive and 23 tested negative for SARS-CoV-2 infection. After a negative COVID-19 test result, 0 patients later tested positive for COVID-19. It is unclear to this reviewer how many of the 23 subjects with a negative test even had a subsequent test conducted.

Overall, this reviewer does not find these analyses, which appear to be preliminary, as informative regarding the frequency or potential clinical relevance of viral RNA (or antigen or virus) rebound following PAXLOVID treatment in "real world" use.

5. CONCLUSIONS

- Based on analyses conducted both by the sponsor and independently by FDA, rebounds in SARS-CoV-2 RNA levels in NP/nasal swab samples were observed in a subset of subjects following treatment with either PAXLOVID or placebo in clinical trial C4671005 (EPIC-HR).
- The likelihood of detecting viral RNA rebound and the percentage of subjects having viral RNA rebound is impacted substantially by the definition, frequency of testing, and number of test results considered.
- In an FDA analysis using a definition which maximizes sensitivity to detect post-treatment viral RNA rebound, post-treatment (i.e., post-Day 5) viral RNA rebound was observed in 8.1% of PAXLOVID recipients and 5.4% of placebo recipients (p=0.02, Fisher's Exact Test).

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- Rates of post-treatment viral RNA rebound were confounded by the greater proportion of Day 5 virologic responders in the PAXLOVID group; post-treatment viral RNA rebound rates were not statistically different (p>0.2) between PAXLOVID and placebo recipients when analyses were restricted to Day 5 virologic responders.
- Rates of post-treatment viral RNA rebound were generally similar for PAXLOVID and placebo recipients across various other analysis timepoints and definitions.
- At each analysis timepoint, in both the treatment and post-treatment periods, a similar or greater percentage of PAXLOVID recipients had viral RNA <LLOQ compared to placebo recipients, regardless of any differences in viral RNA rebound rates.
- Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28.
- Post-treatment viral RNA rebound was not associated with immunosuppression risk or HIV-1 infection, although there were few such subjects for analysis (n=14; 13 immunosuppressed, 1 HIV-1).
- Post-treatment viral RNA rebound was not associated with PAXLOVID treatment-emergent resistance.
- In an analysis conducted by the sponsor, post-treatment viral RNA rebound was not associated with NIR plasma exposures.
- Based on another analysis conducted by the sponsor, post-treatment viral RNA rebound was not associated with recurrence of moderate-severe symptoms.
- Preliminary analyses of a “real-world” electronic health record database generally were not informative regarding the frequency and potential clinical relevance of viral rebound following PAXLOVID treatment.
- Additional resistance analyses are ongoing.

6. LIMITATIONS AND OTHER COMMENTS

- The analyses described in this review were primarily virology-centric analyses focused on SARS-CoV-2 RNA levels in NP swab samples.
- Viral RNA levels may vary in other upper respiratory tract sites, and in clinical practice, NP sampling is presumably less common. Non-NP sampling sites in the upper respiratory tract may be less sensitive for detection and quantification of SARS-CoV-2 RNA shedding.
- These analyses were not based on other body compartments that are important in viral pathogenesis, such as the lungs or other non-respiratory tissues. It should not be assumed that viral RNA levels in NP swabs are directly correlated with viral RNA levels in other body compartments.
- None of these analyses were based on SARS-CoV-2 antigen testing. Rapid antigen tests are commonly self-administered and are also less sensitive than RT-PCR analyses of NP swab samples.
- Measures of viral RNA or viral antigen do not necessarily reflect culturable virus or virus that is able to transmit to others. Viral RNA does not necessarily reflect fully replication competent virus, and a post-treatment increase in viral RNA level in NP samples by itself does not necessarily indicate a “relapse” in viral infection. The sponsor is in the process of assessing for the presence of cell culture infectious virus in NP swab samples from C4671005.
- Analyses of recurrence of mild symptoms in C4671005 have not yet been conducted or reported, although the review team has requested such analyses by the sponsor. These analyses are important

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to understand the clinical relevance of viral RNA rebound; however, they will likely be challenging due to a lack of objective, standardized measures for identifying and quantifying mild COVID-19 symptoms.

- Clinical trial C4671005 was conducted in an unvaccinated population, and ~99% of subjects enrolled in the trial with available viral sequencing data were infected with a SARS-CoV-2 Delta variant. Although nirmatrelvir has been shown to retain activity against other SARS-CoV-2 variants, including Omicron and various Omicron sub-lineages, it is unknown if the frequency or clinical relevance of post-treatment viral RNA rebound varies by vaccination status or infection with different SARS-CoV-2 variants.
- The sponsor plans to conduct a clinical trial, C4671042, to investigate further the clinical relevance of post-treatment viral RNA rebound and the potential benefit of PAXLOVID re-treatment in such cases (see also Clinical Virology review of SDN 134).
- In addition, the sponsor is planning another trial, C4671034, which will evaluate different durations of PAXLOVID treatment in immunocompromised patients with COVID-19. This trial may help to inform the potential benefit of a longer PAXLOVID treatment duration both in terms of clinical outcomes as well as the prevention of post-treatment viral rebound (see also Clinical Virology review of IND 153517 SDNs 222/223).

7. PROPOSED EDITS TO PAXLOVID FACT SHEET FOR HEALTHCARE PROVIDERS

Based on the analyses and conclusions from this review, we proposed including new text in the PAXLOVID EUA Fact Sheet for Healthcare Providers to summarize the post-treatment viral RNA rebound results from the EPIC-HR trial. The following text was added to Section 12.4 Microbiology and agreed upon between the sponsor and FDA. Note that we had originally proposed quoting specific rates of post-treatment viral RNA rebound based on 1 or 2 different analysis definitions, but the sponsor and FDA aligned on not quoting a specific rate due to the variability in viral RNA rebound rates according to different definitions, the anticipated variability in viral RNA rebound rates identified by different assays used in trials and clinical practice, and the potential for misinterpretation that the rates reflect symptomatic COVID-19 rebound, which was not measured in these analyses.

Final agreed upon language:

Viral RNA Rebound

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

Patrick R. Harrington, Ph.D.
Clinical Virology Reviewer

CONCURRENCES

_____**Date:** _____
DAV/Clin Virol TL/J O'Rear

cc: DAV/RPM/Moruf

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PATRICK R HARRINGTON
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JULIAN J O REAR
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Document 2C.15

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (July 6, 2022)

Document URL

https://www.fda.gov/media/159695/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	July 6, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets and Other Documents

On December 22, 2021, the United States Food and Drug Administration (FDA or Agency) authorized PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. PAXLOVID is not currently approved for any use, including treatment of COVID-19.

At the time FDA initially issued the Emergency Use Authorization (EUA), the Agency limited the prescribing of PAXLOVID for an individual patient to physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).[1] This limitation was included to ensure appropriate prescribing of PAXLOVID under the EUA, which requires appropriate patient assessment to confirm the patient meets the eligibility criteria for receiving PAXLOVID. Prescribing of PAXLOVID also requires an assessment of renal and hepatic function and potential drug interactions, which may necessitate clinical management of other medications. This may include a temporary discontinuation, dose modification and/or increased therapeutic monitoring of other medications.

While there were limited supplies of PAXLOVID at the time it was initially authorized, supply has increased substantially and there is now ample supply of PAXLOVID. As of June 26, 2022, the United States Government (USG) has distributed approximately 3.9 million treatment courses of PAXLOVID and approximately 1.8 million treatment courses have been administered for the treatment of COVID-19 under its EUA.[2]

As part of its ongoing review of the circumstances and appropriateness of the EUA for PAXLOVID[3], which included inter-Agency consultation within the USG and consideration of input received from other stakeholders, the Agency recommends revising the EUA for PAXLOVID to authorize the prescribing of PAXLOVID by state-licensed pharmacists in certain circumstances. Specifically, as revised, state-licensed

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[1] Under the Ninth Amendment to the Secretary's PREP Act Declaration, a pharmacist is only allowed to order COVID-19 therapeutics under the terms of the FDA EUA issued for that product. For example, if the EUA includes a condition that the product may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which the belongs, the Ninth Amendment to the Secretary's PREP Act Declaration would not permit pharmacists to order the product. *See* https://www.federalregister.gov/documents/2021/09/14/2021-19790/ninth-amendment-to-declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical

[2] https://aspr.hhs.gov/COVID-19/Therapeutics/orders/Pages/default.aspx

[3] See generally section 564(g) of the Federal Food, Drug and Cosmetic Act.

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pharmacists may prescribe PAXLOVID for an individual patient under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The Agency believes that authorizing state-licensed pharmacists to prescribe PAXLOVID as described above may provide more timely treatment for some patients who are eligible to receive PAXLOVID for the treatment of COVID-19.

State-licensed pharmacists are not authorized to prescribe PAXLOVID when sufficient information consistent with the above is not available at the time of patient assessment. In such instances, the state-licensed pharmacist should refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs for further clinical evaluation. The state-licensed pharmacist should also refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs when an adjustment to another medication is needed due to a potential drug interaction, or when PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible. Referral in such instances will ensure appropriate clinical management of the individual, including consideration of other therapeutics approved or authorized by FDA for the same uses as PAXLOVID

Based on the above, the letter of authorization and the Fact Sheet for Healthcare Providers will be revised as described below:

Summary of Revisions to the Letter of Authorization:

Section 2 (Scope of Authorization) will be revised to state the following:

> *"PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.*
>
> *PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:*

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- *Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and*
- *Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.*

Summary of Revisions to the Fact Sheet for Healthcare Providers:

Section 1 of the Fact Sheet for Healthcare Providers, under "LIMITATIONS OF AUTHORIZED USE", will be revised to authorize prescribing of PAXLOVID by state-licensed pharmacists under certain conditions. The following language will be added to this section, with similar revisions made to the highlights section of the Fact Sheet for Healthcare Providers:

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- *Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and*
- *Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.*

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- *Sufficient information is not available to assess renal and hepatic function.*
- *Sufficient information is not available to assess for a potential drug interaction.*
- *Modification of other medications is needed due to a potential drug interaction.*

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- *PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.*

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health.

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DEBRA B BIRNKRANT
07/06/2022 09:13:54 AM

JOHN J FARLEY
07/06/2022 09:23:19 AM

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U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (August 5, 2022)

Document URL

https://www.fda.gov/media/161018/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	August 5, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
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Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions:

Revisions to the Letter of Authorization: Based on the dosing regimen studied in EPIC-HR, the clinical trial supporting the PAXLOVID EUA, the Fact Sheet for Healthcare Providers and the Letter of Authorization state that PAXLOVID is not authorized for use longer than 5 consecutive days. The Fact Sheet for Healthcare Providers also specifies that PAXLOVID should be initiated within 5 days of symptom onset. However, since PAXLOVID was first authorized in December 2021, several data gaps related to the dosing recommendations in specific populations have been identified.

The first data gap relates to use of PAXLOVID for treatment of COVID-19 in patients with moderate to severe immunocompromise, for whom there have been multiple reports of persistent or prolonged SARS-CoV-2 infection[1]. Less than one percent of subjects in EPIC-HR were classified as having immunosuppression, so data in this population with the recommended dosing regimen are very limited. Furthermore, there are no clinical trial data investigating whether initiation of PAXLOVID treatment beyond 5 days after symptom onset, or a longer duration of PAXLOVID treatment, would be beneficial in this population. Consequently, we initiated discussions with the Sponsor in April 2022 regarding conducting a clinical trial in immunocompromised patients with COVID-19 to investigate different durations of PAXLOVID treatment as well as initiation of PAXLOVID treatment beyond five days after symptom onset. This trial, C4671034, has just begun. Given the importance of obtaining these data, the Letter of Authorization is being amended to include topline data from this study by September 30, 2023, as a condition of authorization.

The second data gap relates to use of PAXLOVID for retreatment of COVID-19 in patients who develop recurrent symptoms and SARS-CoV-2 viral positivity, following initial improvement/resolution, shortly after completing a course of PAXLOVID. "COVID-19 rebound" is a phenomenon which has been reported widely in the press and social media. An analysis of data from EPIC-HR showed that viral rebounds, irrespective of COVID-19 symptoms, were seen with similar rates in PAXLOVID-treated and placebo-treated recipients and were not associated with COVID-19-related hospitalization, death, or development of PAXLOVID drug resistance[2]. Case reports of "COVID-19 rebound" after PAXLOVID treatment indicate that the disease course is usually mild and resolves without further treatment[3], but data are limited. Based on media reports, some health care providers have prescribed a retreatment course of PALOVID for patients with "COVID-19 rebound". As randomized trial data concerning retreatment are needed, we initiated discussions with the Sponsor in May 2022

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[1] Recent review: Laracy JC, Kamboj M, Vardhana SA. Long and persistent COVID-19 in patients with hematologic malignancies: from bench to bedside. Curr Opin Infect Dis. 2022 Aug 1;35(4):271-279.

[2] See the publicly available Clinical Virology Review attached to the EUA memorandum here: https://www.fda.gov/media/159724/download.

[3] Alshanqeeti S, Bhargava A. COVID-19 Rebound After Paxlovid Treatment: A Case Series and Review of Literature. Cureus. 2022 Jun 23;14(6):e26239.

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regarding conducting a clinical trial to evaluate retreatment with PAXLOVID versus placebo in patients who develop "COVID-19 rebound" after an initial PAXLOVID treatment course. Multiple discussions with the Sponsor on optimizing study design in the draft protocols have ensued, and the final protocol for the double-blind, randomized, placebo-controlled trial C4671042 is expected this month. Given the importance of obtaining retreatment data, the Letter of Authorization is being amended to include topline data from this study by September 30, 2023, as a condition of authorization.

Revisions to the Fact Sheet for Patients, Parents, and Caregivers: These revisions are being made to reduce medication errors involving PAXLOVID, which could lead to ineffective therapy and theoretically to serious adverse events. There have been ongoing reports of PAXLOVID wrong dose medication errors, including inappropriate use of renal dosing versus regular dosing and patient errors related to confusion regarding the instructions in labeling and on packaging. Errors have been reported in the prescribing, dispensing, and patient administration phases of PAXLOVID use. In addition, reports have been received about potential packaging quality issues that are similar to the medication error reports. At this time, there is a lack of conclusive evidence as to whether packaging issues are a contributing factor to the ongoing reports. Consequently, the patient fact sheet revisions, along with the issuance of the Dear Health Care Provider letter which informs providers of the ongoing wrong dose medication errors occurring with PAXLOVID and steps to take to avert these errors, are being done to provide additional prescriber and patient education about the correct administration of PAXLOVID.

Summary of Revisions:

- Letter of Authorization: the following two conditions of authorization are being added:
    1. Pfizer will conduct a randomized placebo-controlled trial in patients with "COVID-19 rebound" following an initial treatment course of PAXLOVID to evaluate a subsequent 5-day treatment course of PAXLOVID. Pfizer will provide topline results by September 30, 2023.
    2. Pfizer will conduct a randomized controlled trial to evaluate different durations of PAXLOVID treatment in immunocompromised patients with mild-to-moderate COVID-19. Pfizer will provide topline results by September 30, 2023.

- Fact Sheet for Patients, Parents, and Caregivers: Revisions include addition of detailed instructions about how to take PAXLOVID and how to report problems with the appearance or packaging of PAXLOVID. Figures that include pictures of packaging and tablets for both dosing configurations have been added for further clarity.

Regulatory Conclusion and Associated Actions:

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The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID.

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U.S. FDA Clinical Pharmacology EUA Summary Review (August 25, 2022)

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https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Clinical Pharmacology EUA Summary Review

EUA Number	105
Sponsor	Pfizer Inc.
Submission Date	July 21, 2022
OCP Reviewer	Cristina Miglis, PharmD, MS, BCPS
OCP Team Leader	Mario Sampson, PharmD
OCP Division/Office	Division of Infectious Disease Pharmacology/Office of Clinical Pharmacology
OND Division/Office	Division of Antivirals/Office of Infectious Disease
Drug Name	PAXLOVID (nirmatrelvir oral tablet co-packaged with ritonavir oral tablet)
Dosage and Administration	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
Indication	Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Rationale for Revisions to EUA Fact Sheets

The PAXLOVID EUA fact sheet was revised as follows:

1. The following edits were made to (b) (4):
   - The Applicant proposed (b) (4) . We recognize there is a clinically significant drug-drug interaction between disopyramide and PAXLOVID and agree with adding disopyramide to the fact sheet. However, we do not agree that the interaction (b) (4). The review team has (b) (4) listed this interaction in Table 1 under the antiarrhythmics drug class with a statement that caution is warranted when co-administered with PAXLOVID, and antiarrhythmic therapeutic concentration monitoring is recommended. The language provided for this drug interaction in the fact sheet is consistent with NORVIR and the boosted protease inhibitors labels. (b) (4) .

- The review team also [redacted]. Further review of the clozapine package insert prompted the review team to move this drug [redacted] to a drug that should be avoided with PAXLOVID based on language in the clozapine USPI stating that patients taking concomitant CYP1A2, CYP2D6, or CYP3A4 inhibitors should be monitored for adverse reactions and a clozapine dose reduction should be considered if necessary.

- Like clozapine, the inclusion of pethidine [redacted]. It should be noted that pethidine is marketed as meperidine in the U.S. [redacted]. We recognize the meperidine label contains a boxed warning for concomitant use with CYP3A4 inhibitors a regarding potentially fatal overdose. This warning is similar to the boxed warning on other narcotic analgesics (fentanyl, hydrocodone or oxycodone) and is not included [redacted] in each respective label. The PAXLOVID factsheet includes a clinical comment in Table 1 recommending careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression when these agents are concomitantly administered with PAXLOVID). Thus, the review team recommended [redacted] the addition of meperidine to the narcotic analgesics class in Table 1.

2. The following edits were made to Table 1 in Section 7.3: Established and Potentially Significant Drug Interactions
   - The following drugs were added based on their inclusion in the NIH guidelines for DDIs with PAXLOVID. Language in Table 1 was added consistent with the concomitant drug label and the NORVIR or boosted protease inhibitor USPIs: Disopyramide, apixaban, clonazepam, cilostazol, saxagliptin, tofacitinib, upadacitinib, darifenacin, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, riociguat, tadalafil.
   - Clozapine was reclassified [redacted] to established and other potentially significant drug interactions.
   - Pethidine was reclassified under its US name, meperidine, with a change [redacted] to established and other potentially significant drug interaction.
   - The PDE 5 inhibitor drug class was changed to Pulmonary Hypertension Agents (PDE 5 inhibitors)
   - The PDE 5 inhibitor drug class was changed to Erectile Dysfunction Agents (PDE 5 inhibitors)

The edits outlined above were also applied to the prescriber checklist which is consistent with the most up to date version of the fact sheet.

Clinical Pharmacology Assessment

The review team's recommended revisions, as described above, were accepted by the applicant (with minor editorial revisions). The final agreed upon language is shown below:

(b) (4)

(b) (4)

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Section 7: Table 1 in Section 7.3

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events *[see Dosage and Administration (2.4)]*.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline	↑ bedaquiline	Refer to the bedaquiline product label for further information.
	rifabutin	↑ rifabutin	Refer to rifabutin product label for further information on rifabutin dose reduction.
	rifapentine	↓ nirmatrelvir/ritonavir	Avoid concomitant use with PAXLOVID.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar clopidogrel cilostazol	↑ aliskiren ↑ ticagrelor ↑ vorapaxar ↓ clopidogrel active metabolite ↑ cilostazol	Avoid concomitant use with PAXLOVID. Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor elexacaftor/tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑elexacaftor/tezacaftor/ivacaftor ↑ tezacaftor/ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.
Endothelin receptor antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir ombitasvir/paritaprevir/ritonavir and dasabuvir sofosbuvir/velpatasvir/voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.
Immunosuppressants	cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid use of PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended. Refer to the individual immunosuppressant product label for further information and obtain expert consultation from the patient's immunosuppressive therapy specialist.
	everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID.
Janus kinase (JAK) inhibitors	tofacitinib, upadacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
		↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID. Refer to individual product label for more information.
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered.

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Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

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Document 2C.18

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (September 26, 2022)

Document URL

https://www.fda.gov/media/165148/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	September 26, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets and Other Documents

The PAXLOVID EUA Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents, and Caregivers are being revised at this time for the following reasons:

1. **To Update the Fact Sheet for Healthcare Providers with Information on SARS-CoV-2 Resistance to Nirmatrelvir in Cell Culture.**

   Recent studies conducted by the sponsor and others[1,2] have identified a number of SARS-CoV-2 M^{pro} substitutions and combinations of M^{pro} substitutions associated with nirmatrelvir resistance in cell culture. Most of these substitutions and combinations of substitutions were not previously included in the PAXLOVID EUA Fact Sheet for Healthcare Providers. Therefore, the "Antiviral Resistance" subsection of Section 12.4 is being revised to provide a summary of SARS-CoV-2 M^{pro} substitutions associated with nirmatrelvir resistance in cell culture. The revisions also highlight the fact that the M^{pro} E166V and L50F+E166V substitutions, which have been associated with nirmatrelvir resistance in cell culture, were identified in three participants treated with PAXLOVID in the pivotal clinical trial EPIC-HR, although these participants did not experience hospitalization or death. The clinical significance of these M^{pro} substitutions is unknown.

2. **To Update the Fact Sheet for Healthcare Providers with Information on Nirmatrelvir Activity Against SARS-CoV-2 Omicron Sub-Variants and Activity Against SARS-CoV-2 in Animal Models.**

   Recent studies conducted by the sponsor have demonstrated that nirmatrelvir retains activity against the Omicron sub-variants BA.2, BA.2.12.1, and BA.4 in cell culture. Therefore, the "Antiviral Activity" subsection of Section 12.4 is being revised to indicate these findings. Other studies have found that nirmatrelvir also retains activity against the Omicron sub-variants BA.2.75 and BA.5 in cell culture. Lastly, the "Antiviral Activity Against SARS-CoV-2 in Animal Models" subsection of Section 12.4 is being revised to provide a summary of results from a new animal study conducted by the sponsor, in which the activity of nirmatrelvir, ritonavir, and nirmatrelvir+ritonavir against mouse-adapted SARS-CoV-2 was investigated in mice.

3. **To Update the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients, Parents, and Caregivers to State that Anaphylaxis has been Reported with PAXLOVID.**

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[1] Iketani, S, Mohri, H, Culbertson, B et al., Multiple Pathways for SARS-CoV-2 Resistance to Nirmatrelvir. bioRxiv. 2022Aug18 (Preprint/not yet peer reviewed) available: https://doi.org/10.1101/2022.08.07.499047

[2] Zhou, Y, Gammeltoft, K, Ryberg, L et al. Nirmatrelvir Resistant SARS-CoV-2 Variants with High Fitness In Vitro. bioRxiv. 2022Jun07 (Preprint/not yet peer reviewed) available: https://doi.org/10.1101/2022.06.06.494921

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The Fact Sheet for Healthcare Providers currently includes the warning and precaution "Allergic Reactions/Hypersensitivity" which states that hypersensitivity reactions have been reported with PAXLOVID and that cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with ritonavir, a component of PAXLOVID. However, since that warning and precaution was added, there have been 14 post-authorization reports indicative of anaphylaxis after PAXLOVID use (reported in FAERS through August 29, 2022). As such, Sections 5.2, 6.2, and 17 of the Fact Sheet for Healthcare Providers are being revised to indicate that anaphylaxis has been reported with PAXLOVID; other small, editorial changes to the language are also being made. Similar updates about anaphylaxis being reported with PAXLOVID use are being added to the Fact Sheet for Patients, Parents, and Caregivers.

Summary of Fact Sheet Revisions:

- Section 5.2 of the Fact Sheet for Healthcare Providers was renamed Hypersensitivity Reactions and now reads as follows:
    - *Anaphylaxis and other hypersensitivity reactions have been reported with PAXLOVID [see Adverse Reactions (6.2)]. Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of PAXLOVID (refer to NORVIR prescribing information). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.*
    - Similar changes were made to Sections 6.2 and 17 of the Fact Sheet for Healthcare Providers as well as to the Fact Sheet for Patients, Parents, and Caregivers.
- Section 12.4 of the Fact Sheet for Healthcare Providers (Microbiology) was modified as follows:
    - The "Antiviral Activity" subsection was revised to indicate that nirmatrelvir had similar activity against SARS-CoV-2 Omicron sub-variants BA.2, BA.12.1, and BA.4 in cell culture compared to previous SARS-CoV-2 variants.
    - The "Antiviral Activity Against SARS-CoV-2 in Animal Models" subsection was revised to add a summary of the sponsor's new study on the activity of nirmatrelvir, ritonavir, and nirmatrelvir+ritonavir against mouse-adapted SARS-CoV-2 in mice.
    - The "Antiviral Resistance" subsection was divided into two subsections: "Antiviral Resistance in Cell Culture and Biochemical Assays" and "Antiviral Resistance in Clinical Trials." The subsection on resistance in cell culture and biochemical assays was revised and now reads as follows:

SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 8 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 8: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitution (EC_{50} value fold change)	*T21I (1.1-4.6), L50F (1.4-4.2), P108S (ND), T135I (ND), F140L (ND), S144A (2.2-2.5), C160F (ND), E166A (3.3), E166V (25-267), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-2.3), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (2.1-5.5).*
≥2 Substitutions (EC_{50} value fold change)	*T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-163), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).*

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold-change based on K_i values) of nirmatrelvir: G15S (4.4), Y54A (24.0), T135I (3.2), F140A (39.0), F140L (5.4), S144A (92.0), S144E (470), S144T (160), H164N (6.4), E166A (33.0), E166G (16.0), H172Y (230), A173V (26.0), V186G (13.0), Q189K (65.0), Q192L (28.0), Q192P (33.0), and D248E (3.7). The clinical significance of these substitutions is unknown.

- The "Antiviral Resistance in Clinical Trials" subsection was revised by adding the following statement: "In one subject with a baseline M^{pro} L50F substitution, the M^{pro} E166V substitution co-occurred with L50F on Day 5 (included in counts above). The M^{pro} E166V and L50F+E166V substitutions have been associated with nirmatrelvir resistance in cell culture (Table 8)." In addition, the following statements were removed: "In a biochemical assay, the P132H/L/S,

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A260V, and A266V M^{pro} substitutions did not reduce nirmatrelvir activity (K_i fold-change ≤1, <1, and ~2, respectively). The potential phenotypic effect on nirmatrelvir susceptibility for the other substitutions is unknown."

  - Minor edits were made to the "Viral RNA Rebound" and "Cross-Resistance" subsections.
- Minor edits were made to Section 14.1 of the Fact Sheet for Healthcare Providers (Clinical Studies) for clarity.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID.

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Document 2C.19

U.S. FDA Memorandum: Summary Basis for Revising Certain Conditions on Printed, Advertising and Promotional Materials (October 27, 2022)

Document URL

https://www.fda.gov/media/162704/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 27, 2022

TO: Administrative files for the Emergency Use Authorizations for baricitinib (EUA 092), Actemra (EUA 099), EVUSHELD (EUA 104), PAXLOVID (EUA 105), Lagevrio (EUA 108), and bebtelovimab (EUA 111)

Subject: Summary Basis for Revising Certain Conditions on Printed, Advertising and Promotional Materials

Background

Under section 564 of the Federal Food, Drug & Cosmetic Act (FD&C Act), the FDA may, pursuant to a declaration by the Health and Human Services Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an Emergency Use Authorization (EUA), the FDA must determine that-

- Based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that –
  - the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; and
  - that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product;
- There are no adequate, approved, and available alternatives.

When issuing an EUA, the Agency will establish conditions on an authorization deemed necessary or appropriate to protect the public health.[1] For example, the Agency will include conditions requiring that health care professionals administering, and individuals to whom the product is administered, be informed of certain information regarding the authorized product. The Agency will also establish conditions on the monitoring and reporting of adverse events related to the emergency use of the product. Under the statutory provisions for EUAs, the Agency may also establish conditions on advertisements and other promotional descriptive printed matter that relate to the emergency use of the authorized product.[2]

1 See section 564(e) of the FD&C Act.
2 See section 564(e)(4) of the FD&C Act.

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The statutory criteria for issuance of an EUA set forth a regulatory and scientific standard that is different from the standard required for FDA's approval of a drug.[3] In many instances, an EUA sponsor continues to develop the drug as a medical countermeasure in parallel with the drug being available under EUA for such investigational use. The flexibility of the EUA statutory provisions is essential to preparing for and responding to a chemical, biological, radiological, or nuclear emergency (CBRN).

To date, the Center for Drug Evaluation and Research (CDER) has included the following condition in the Letter of Authorization for COVID-19 therapeutics[4] relating to "Printed Matter, Advertising, and Promotional Materials":

> No descriptive printed matter, advertising, or promotional materials relating to the use of Drug X under this authorization may represent or suggest that Drug X is safe or effective when used for <<authorized use>>.

This condition, in combination with other conditions on advertising and promotion currently included in EUAs for COVID-19 therapeutics, already authorize the dissemination of product-specific, truthful, and non-misleading information relating to the use of the product when consistent with the authorized labeling. Current conditions on advertising and promotional materials included in EUAs for COVID-19 therapeutics require that any such materials clearly and conspicuously state that the product (or use) is not FDA-approved, but rather has been authorized for such use for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked.

CDER was recently made aware that there may be benefit in clarifying the condition referenced above for EUA sponsors that wish to include in promotional materials information about the safety and efficacy data that supported the issuance of a particular EUA -- for example, in promotional materials disseminated to health care providers and patients. CDER has considered this and has determined that it is appropriate to make clarifying revisions to the above-referenced EUAs as further described below.

Revisions to Condition(s) on Advertising and Promotion

The Agency's understanding of COVID-19 and its impact on the public health has greatly increased during the COVID-19 public health emergency. As we've observed, the epidemiological landscape for COVID-19, specifically with emerging viral variants of SARS-CoV-2, has shifted multiple times and in a few instances, relatively quickly. In addition, the rates of infection and public health impact of the virus continues to change. Each of these factors has contributed to a shifting clinical context which healthcare providers and patients, alike, should be

3 FDA approval of a drug requires, in part, substantial evidence of effectiveness and a demonstration of safety. See section 505(d) of the FD&C Act (21 USC 355(d)).
4 For the purposes of this memo, the term "COVID-19 therapeutics" refers to drugs authorized for the prevention or treatment of COVID-19 under the recommendation by CDER scientific and regulatory staff.

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aware; underscoring the importance for accurate and non-misleading information on the authorized COVID-19 therapeutics being available to advance the public health.

While the authorized labeling for an EUA should serve as the primary resource for information on the authorized product, dissemination of truthful and non-misleading printed matter, advertising, and promotional materials containing scientific information related to the authorized use of the product, when consistent with the terms and conditions of the respective authorization, can further enhance the public's awareness of and understanding on the authorized COVID-19 therapeutic.

As such, the Agency believes that it is appropriate[5] to revise certain conditions on "Printed Matter, Advertising, and Promotion" in the currently authorized EUAs for COVID-19 therapeutics to replace the condition referenced above with the following language:

> Company A may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of DRUG X that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Company A may not imply that DRUG X is FDA approved by making statements such as "DRUG X is safe and effective for <<authorized use>>."

This section in the respective LOAs will also be revised to require that such materials be submitted to the Agency for consideration at least 14 calendar days prior to initial dissemination or first use.[6]

The Agency has determined that the revisions described above are appropriate to protect the public health or safety. These revisions clarify that the inclusion of accurate descriptions of safety and efficacy information that underly the issuance of a particular EUA in printed matter, advertising and promotional materials is authorized. Additionally, the submission of these materials to the Agency prior to initial dissemination or first use will provide CDER the opportunity to provide feedback on the submitted materials, as appropriate, to ensure consistency with the terms and conditions of the EUA, including the authorized labeling.

As noted above, FDA's authorization of a drug for emergency use under an EUA is not the same as FDA approval. When issuing an EUA, the Agency makes scientifically-based regulatory determinations on the known and potential benefits and risks of a product based on the totality of scientific information available during, or when there is a significant potential for a CBRN emergency. As such, there may be uncertainties regarding the safety and effectiveness data supporting an EUA for COVID-19 therapeutics. Accordingly, the Agency is also clarifying that printed, advertising and promotional materials need to include a description of any limitations of

5 See section 564(g)(2)(C) of the FD&C Act.
6 FDA's intention is to prioritize feedback to sponsors of EUAs during the 14-day period when significant issues are identified.

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the clinical trial data, consistent with the limitations described in the authorized labeling.[7] The inclusion of this information, along with other information required under the conditions on printed matter, advertising and promotional materials, is necessary to facilitate health care providers and patients in making informed decisions on the use of the authorized COVID-19 therapeutics.

The Agency will continue to assess the circumstances and appropriateness of each EUA covering an authorized COVID-19 therapeutic and will make additional revisions, when appropriate.

Peter P. Stein -S

Digitally signed by Peter P. Stein -S
Date: 2022.10.27 13:57:27 -04'00'

Peter Stein, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

7 See section 564(e)(1)(A)(i)(II) and section 564(e)(1)(A)(ii)(II)

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Document 2C.20

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)

Document URL

https://www.fda.gov/media/165227/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	February 1, 2023
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets and Other Documents

The PAXLOVID EUA Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents, and Caregivers; and Letter of Authorization are being revised at this time for the following reasons:

1. **To update the drug-drug interaction information in the Fact Sheet for Healthcare Providers with the addition of Verapamil**

   In the FDA Adverse Event Reporting System, since the initial authorization of PAXLOVID and through January 2, 2023, the Division of Pharmacovigilance has identified six cases reporting a drug-drug interaction when verapamil was co-administered with PAXLOVID. Bradycardia and hypotension were the most commonly reported adverse events. Three of the six cases reported admission to an intensive care or critical care unit following the interaction, including two cases which reported the need for pharmacologic treatment (e.g., atropine, dopamine, norepinephrine). In one of these two cases, the patient eventually needed intubation. No outcome was reported in this case, however, a separate case describing fatal cardiogenic shock following treatment with PAXLOVID and verapamil was identified, and it was suspected that this is the same case and therefore, was not included in the total number of cases.

   Since the initial authorization for PAXLOVID, the priority in adding drugs to the PAXLOVID Fact Sheet for Healthcare Providers drug interactions table, beyond what the Sponsor proposed, has been on those recommended to be held or dose-adjusted when administered with PAXLOVID. The Fact Sheet for Healthcare Providers includes statements that the list of drugs included in the drug interactions table is not intended to be comprehensive. Other resources for drug-drug interactions are available and have included information on the drug interaction between verapamil and ritonavir, including the ritonavir (NORVIR) USPI, the NIH COVID-19 Treatment Guidelines list of drug-drug interactions with PAXLOVID in the “Continue Concomitant Medication and Monitor for Adverse Effects” category, and other online resources such as University of Liverpool COVID-19 Drug Interactions Checker (https://www.covid19-druginteractions.org/checker). Verapamil is not currently included in the list of calcium channel blockers in the drug interactions table in the PAXLOVID Fact Sheet for Healthcare Providers.

   As with all EUAs, the Agency regularly reviews information and data associated with the use of the product under its authorization and will revise and update the EUA, when appropriate. Therefore, FDA is adding verapamil to the table of drug interactions in the PAXLOVID Fact Sheet for Healthcare Providers. Similar

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revisions are being made to the Patient Eligibility Screening Checklist Tool for Prescribers for consistency with the Fact Sheet for Healthcare Providers.

2. **To revise the indication to remove the wording related to positive SARS-Cov-2 testing in the Fact Sheet for Healthcare Providers; the Fact Sheet for Patients, Parents, and Caregivers; and the Letter of Authorization**

   The Agency has determined the wording "*with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing*" is not needed for Section 1: Emergency Use Authorization. We are removing the wording related to positive SARS-CoV-2 testing to provide flexibility in making a clinical diagnosis of COVID-19 in some scenarios where doing so may be appropriate. However, we continue to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

   While a positive direct SARS-CoV-2 viral test generally should be available as part of diagnosing a patient with mild to moderate COVID-19, the sensitivity of antigen testing is lower than RT-PCR testing and in rare cases, timing of the availability of testing may justify making a diagnosis of COVID-19 prior to the availability of a positive test result. For example, a patient at high risk for disease progression and death presents with symptoms consistent with COVID-19, has a known exposure such as another person in the household with a positive direct SARS-CoV-2 viral test, but the patient has a negative antigen test and is awaiting RT-PCR results.

   In a study by Chu et al., among 225 adults and children with RT-PCR confirmed SARS-CoV-2 infection, antigen test sensitivity was 64% when compared with same-day RT-PCR. Antigen test sensitivity peaked on day 4 of illness at 77%.[1] Therefore, it is important to allow healthcare providers flexibility to consider the clinical context to aid in early COVID-19 diagnosis. This may be especially important for immunocompromised patients who may be at particularly high risk for progression to severe disease in the absence of timely treatment initiation.

   Similar revisions are being made to the Patient Eligibility Screening Checklist Tool for Prescribers for consistency with the Fact Sheet for Healthcare Providers.

3. **To update the information on VEKLURY in the Fact Sheet for Healthcare Providers**

   With this update, the information regarding available alternates for the EUA authorized use has been updated in relation to VEKLURY (remdesivir) to align with the most recent VEKLURY USPI.

[1] Chu VT et al. Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection. JAMA Intern Med. 2022 Jul 1;182(7):701-709.

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4. **To revise the Letter of Authorization to remove a condition of authorization that has been satisfied**

   The Letter of Authorization contained a condition of authorization related to completion of analyses of SARS-CoV-2 shedding and nucleotide sequencing from the EPIC-HR clinical trial. The requested final reports, datasets, and related follow-up communications were submitted. With these submissions the EUA condition has been satisfied, and therefore this condition of authorization is being removed.

Summary of Revisions:

- Section 1 of the Fact Sheet for Healthcare Providers (EMERGENCY USE AUTHORIZATION) was updated to:
  - Update the authorized use to: "the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death."
  - Update the Information Regarding Available Alternatives to the EUA Authorized Use to state that age range for the approved VEKLURY mild-to-moderate COVID-19 treatment indication is 28 days and older weighing at least 3 kg, and to remove the statement in the VEKLURY indication about needing positive results of direct SARS-CoV-2 viral testing.
- Section 7.3 of the Fact Sheet for Healthcare Providers (Established and Other Potentially Significant Drug Interactions) was modified to add verapamil to Table 1 as a calcium channel blocker with a DDI.

In addition, the Fact Sheet for Patients, Parents, and Caregivers; the Letter of Authorization; and the Patient Eligibility Screening Checklist Tool for Prescribers were revised as needed for consistency with the above changes.

- Finally, Section III.O of the Letter of Authorization was revised to remove the following condition of authorization:
  - *Pfizer must complete analyses of SARS-CoV-2 shedding and nucleotide sequencing from the EPIC-HR clinical trial. Viral sequencing analyses should be conducted for all clinical samples with sufficient viral RNA levels, including samples collected at baseline, on-treatment and post-treatment, to identify and characterize the potential emergence or persistence of amino acid changes associated with PAXLOVID treatment. Pfizer must submit preliminary reports of these analyses by July 31, 2022, and final reports, including complete SARS-CoV-2 RNA and infectivity analyses, NGS quality control assessments, analysis-ready datasets, and final raw fastq NGS datasets by December 31, 2022.*

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Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID. The analysis of benefits and risks that underlies the authorization of EUA 105 remains unchanged.

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Document 2C.21

U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (May 25, 2023)

Document URL

https://www.fda.gov/media/168528/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

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Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research (CDER) Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	May 25, 2023
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2. Ritonavir is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Rationale for Revisions to EUA Fact Sheets and Other Documents

The PAXLOVID Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents, and Caregivers; and Letter of Authorization (LOA) are being revised at this time based on the review of information submitted as part of the New Drug Application (NDA) 217188 and, relatedly, the FDA approval of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization and death.

PAXLOVID received FDA approval on May 25, 2023, for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization and death. The revised PAXLOVID EUA will continue to authorize PAXLOVID for emergency use to treat certain eligible pediatric patients, a patient population that is not covered under the approved NDA for PAXLOVID at this time. PAXLOVID will also remain authorized under EUA to ensure continued access for all eligible patients to the U.S. government's supply of PAXLOVID, including adult patients who are the subject of the approved NDA, pending sufficient availability of the approved product.[1]

Based on the FDA approval of PAXLOVID, including the review of information submitted in the NDA, the EUA documents are being revised to align, when appropriate, with the FDA-approved United States Prescribing Information (USPI). Notably, the authorized Fact Sheet for Healthcare Providers is being revised to include a boxed warning to better communicate the risk of significant drug-drug interactions (DDIs) with PAXLOVID. Serious adverse reactions due to DDIs are the key safety concern with use of PAXLOVID. Safety surveillance data obtained under the EUA, which were discussed at the Antimicrobial Drugs Advisory Committee Meeting about PAXLOVID on March 16, 2023, indicate the following:

1. Greater than 50% of PAXLOVID-eligible Medicare and VA patients are taking medications that have a DDI with PAXLOVID. FDA noted that many of these DDIs could be prevented or managed with dose modification, interruption, and/or additional monitoring.
2. Most PAXLOVID prescriptions were written by adult primary care providers, who may not be familiar with managing potential DDIs with ritonavir, which is more commonly prescribed by infectious disease physicians and other specialists.
3. More than 250 cases of serious adverse events reported to the FDA Adverse Event Reporting System (FAERS) have been assessed as being possibly or probably related to PAXLOVID DDIs included in the Fact Sheet for Healthcare Providers, including 6 with a fatal outcome. Reports of serious adverse events

[1] Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of this EUA.

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due to DDIs have continued despite previous risk mitigation efforts (e.g., the existing Warning and Precaution about the risk of serious adverse reactions due to DDIs, several Dear Healthcare Provider Letters, the Patient Eligibility Screening Checklist Tool for Prescribers, information on the risk of DDIs in the PAXLOVID FAQ and CDER conversation on the FDA website, and external outreach efforts).

For these reasons, and with supportive advice from the CDER Medical Policy and Program Review Council, a boxed warning to highlight this important safety risk is being added to the Fact Sheet for Healthcare Providers. Please see the NDA 217188 (PAXLOVID) integrated review for details on the submitted information, data analyses, and assessments that supported both the boxed warning and the other changes.

The following represent key differences between the EUA documents, including the authorized Fact Sheets, and the PAXLOVID approval, including the FDA-approved USPI:

1) The EUA documents, including the authorized Fact Sheets, will continue authorizing PAXLOVID for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death[2]. As noted above, this patient population is not covered under the approved NDA for PAXLOVID at this time.
2) The EUA documents, including the authorized Fact Sheets, will continue authorizing PAXLOVID for the treatment of mild-to-moderate COVID-19 in adult patients who are at high risk for progression to severe COVID-19, while the USPI will explain that PAXLOVID is approved for this use.
3) The EUA documents, including the authorized Fact Sheets, will retain the existing limitations of authorized use, including those related to PAXLOVID not being authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 or for use longer than 5 consecutive days.[3]
4) The EUA documents, including the authorized Fact Sheets, will continue authorizing state-licensed pharmacists to prescribe the authorized PAXLOVID, subject to certain terms and conditions.
5) Section 16 of the authorized Fact Sheet for Healthcare Providers will only describe the presentations of PAXLOVID manufactured and labeled for use under the EUA. The United States Government inventory of PAXLOVID, which is

[2] At the time of this action, Pfizer's clinical development of PAXLOVID for use in the pediatric population remains ongoing.

[3] Although not included as a limitation of use in the FDA-approved USPI, PAXLOVID is not approved for the initiation of treatment in patients requiring hospitalization due to severe COVID-19, and the recommended dosage remains for 5 consecutive days.

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currently the sole source of PAXLOVID available for distribution in the United States, is comprised solely of these presentations.[4]

6) The authorized Fact Sheet for Patients, Parents, and Caregivers will only provide illustrations of the presentations of PAXLOVID manufactured and labeled for use under the EUA.
7) The authorized Fact Sheet for Patients, Parents and Caregivers now provides instructions on how to obtain information on shelf-life extensions for PAXLOVID.[5]
8) The authorized Fact Sheets will continue including any general information on EUAs (i.e., not product-specific to PAXLOVID).

The LOA has been revised to remove certain conditions requiring the collection and analysis of data related to PAXLOVID. These conditions are the subject of postmarketing requirements or postmarketing commitments, as appropriate, now associated with the approval of NDA 217188. These conditions were removed from the EUA to avoid unnecessary redundancy. The condition requiring that Pfizer conduct ongoing virologic monitoring has been retained, but was revised to be consistent with the language in a corresponding postmarketing requirement for the NDA; this will ensure continued monitoring for the emergence of PAXLOVID-resistant SARS-CoV-2 until the FDA-approved presentations of PAXLOVID are available.

Lastly, the LOA retains certain conditions or requirements that FDA considers necessary or appropriate to protect the public health, in light of the fact that PAXLOVID under the EUA will be used in a broader population than the population approved under the NDA. For example, the LOA retains a requirement that Pfizer recall product if requested by FDA, under certain circumstances.[6]

Summary of Specific Revisions:

- In the Fact Sheet for Healthcare Providers, revisions were made in the highlights, before Section 1 (addition of a boxed warning), and in Sections 1, 2, 4, 5, 6, 7, 8, 12, 13, 14, and 17. Key revisions include the following:
  - Addition of a boxed warning about significant DDIs with PAXLOVID, and revisions to the language about DDIs in Sections 4, 5, and 7 to better communicate this risk and the actions that can be taken to mitigate this risk.
  - Revisions to Section 1 to address the amended HHS determination underlying the EUA declaration for drugs and biological products, dated March 15, 2023, and to update the information on approved alternatives for

[4] Likewise, Section 16 of the FDA-approved USPI only describes the approved presentations of PAXLOVID.

[5] FDA has received several FAERS case reports between March 31, 2023 and May 11, 2023 that describe patient confusion regarding PAXLOVID expiration date extensions. The cases suggest that healthcare providers are aware of the extension, but this information is not being communicated to patients. For example, cases have described patient concerns about taking an “expired” product and have resulted in patients refusing to take PAXLOVID or discontinuing PAXLOVID upon discovery of the labelled expiration date. Cases also reported patients calling the pharmacy, where they were informed of the expiration date extension.

[6] See condition H in the Letter of Authorization for PAXLOVID.

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the EUA authorized use to incorporate information about the approved PAXLOVID product and why adults are still included under the EUA.
  - Addition of rifapentine to the list of contraindicated medications with PAXLOVID (rifapentine was previously included in Table 1 with a recommendation of "avoid concomitant use with PAXLOVID").
  - Revisions to the adverse reactions listed in Section 6 based on the full clinical trial data (hypertension and myalgia are no longer included as adverse reactions under clinical trials experience; hypertension, headache, vomiting, toxic epidermal necrolysis, and Steven's Johnson syndrome are now included as adverse reactions identified during post-authorization use of PAXLOVID).
  - Revisions to Section 12, Clinical Pharmacology, based on analyses of additional clinical trial data, including addition of Section 12.2 with results from a cardiac electrophysiology analysis and revisions to the virology data in section 12.4.
  - Revisions to the efficacy data from EPIC-HR in Section 14, as well as addition of data from two additional clinical trials.

- The Fact Sheet for Patients, Parents, and Caregivers was revised throughout for consistency with the changes to the Fact Sheet for Healthcare Providers listed above. In addition, the following new section was added:
  - ***What if I have questions about the expiration date for my PAXLOVID?*** *The FDA has extended the expiration date (shelf-life) for some lots of PAXLOVID. To find the extended expiration date, enter the lot number found on the side of carton or bottom of blister pack at this website: https://www.paxlovidlotexpiry.com/ or talk with your healthcare provider. Information on the authorized shelf-life extensions for PAXLOVID may also be found at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/expiration-dating-extension.*

- The LOA was revised with language related to the new approval of PAXLOVID for adults. In addition, the following changes were made to the conditions of authorization:
  - The following conditions were removed:
    - *Condition M: FDA may require Pfizer to assess the activity of the authorized PAXLOVID against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Pfizer will perform the required assessment in a manner and timeframe agreed upon by Pfizer and the Agency. Pfizer will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Pfizer will submit any relevant proposal(s) to revise the authorized labeling based on the results of its*

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assessment, as may be necessary or appropriate based on the foregoing assessment.

- *Condition O.1: Pfizer must conduct cell culture phenotypic analyses of recombinant SARS-CoV-2 viruses or replicons carrying specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies, or polymorphisms emerging in novel SARS-CoV-2 variants. Specific amino acid changes that should be characterized include the following:*
  - *amino acid changes associated with reduced nirmatrelvir susceptibility in biochemical assays,*
  - *natural amino acid polymorphisms in Mpro that come in contact with or in close proximity (<5 Å) to bound nirmatrelvir,*
  - *amino acid changes associated with nirmatrelvir/ritonavir treatment emergence, treatment failure, or prolonged virologic shedding or rebound in clinical trials, and*
  - *amino acid polymorphisms identified in resistance surveillance analyses.*

  Amino acid changes in both Mpro and Mpro cleavage sites should be considered in these analyses. Specific amino acid changes of interest for phenotypic characterization in cell culture assays currently include Mpro substitutions Y54A, E55L, F140A, S144A, E166A, H172Y, Q189K, and A260V. When warranted due to technical challenges, alternative approaches to the requested cell culture assays will be considered on a case-by-case basis. Pfizer must submit an updated summary report no later than July 31, 2022 for any currently ongoing studies, and at least every 6 months thereafter as additional data accumulate.
- *Condition O.2: Pfizer will provide topline results from a safety and pharmacokinetic study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis) no later than February 28, 2023.*
- *Condition O.3: Pfizer will conduct a randomized placebo-controlled trial in patients with "COVID-19 rebound" following an initial treatment course of PAXLOVID to evaluate a subsequent 5-day treatment course of PAXLOVID. Pfizer will provide topline results by September 30, 2023.*
- *Condition O.4: Pfizer will conduct a randomized controlled trial to evaluate different durations of PAXLOVID treatment in immunocompromised patients with mild-to-moderate COVID-19. Pfizer will provide topline results by September 30, 2023.*

- The former Condition L was revised to read as follows:

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- *Pfizer will 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. Pfizer will conduct these surveillance activities on at least a monthly basis and submit reports to FDA on these surveillance activities on a quarterly basis. In these reports, Pfizer will 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).*
- *Pfizer will also 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. Pfizer will 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.*

In addition, the Patient Eligibility Screening Checklist Tool for Prescribers was revised as needed for consistency with the changes to the Fact Sheets.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommend revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID.

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