

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: [REDACTED] (b) (6) Phone: [REDACTED] (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	<u>Nirmatrelvir</u> 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. <u>Ritonavir</u> 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.

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 infection¹. 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 resistance². Case reports of “COVID-19 rebound” after PAXLOVID treatment indicate that the disease course is usually mild and resolves without further treatment³, but data are limited. Based on media reports, some health care providers have prescribed a retreatment course of PAXLOVID for patients with “COVID-19 rebound”. As randomized trial data concerning retreatment are needed, we initiated discussions with the Sponsor in May 2022

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.

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:

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.

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/

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