

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	<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 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.

## 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

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%.<sup>1</sup> 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.

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<sup>1</sup> 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.

#### 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.*

**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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/s/  
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