

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	<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 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<sub>50</sub> 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<sub>50</sub> 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<sub>i</sub> 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

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.

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).*

*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](http://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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