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.

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.

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.

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.

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*

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:

- *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.

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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