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	November 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 mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death. See Letter of Authorization.

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 the Letter of Authorization (LOA) and EUA Fact Sheets

Availability of NDA-labeled PAXLOVID

On October 30, 2023, Pfizer announced that PAXLOVID labeled and packaged in accordance with the approved New Drug Application 217188 (NDA-labeled PAXLOVID) will be available beginning November 1, 2023.[1] The Administration for Strategic Preparedness and Response in the U.S. Department of Health and Human Services has also announced its transition from and winding down of the U.S. government's distribution of PAXLOVID that is labeled and packaged in accordance with the Emergency Use Authorization (EUA-labeled PAXLOVID).[2]

To facilitate this transition, the Division of Antivirals (DAV) in the Office of Infectious Diseases recommends revising the EUA for PAXLOVID to authorize NDA-labeled PAXLOVID 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.

To ensure continued patient access to PAXLOVID during this transition, DAV also recommends that the EUA for PAXLOVID continue to authorize EUA-labeled PAXLOVID for the treatment of 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.[3]

During this transition, the EUA-labeled PAXLOVID and NDA-labeled PAXLOVID will be simultaneously in distribution and available for dispensing. The EUA-labeled PAXLOVID and NDA-labeled PAXLOVID contain the same tablets (nirmatrelvir and ritonavir). Since PAXLOVID was initially authorized for emergency use, Pfizer has been required, as a condition under the EUA, to comply with the same good manufacturing practices that apply to approved products when manufacturing EUA-labeled PAXLOVID. Based on these considerations, it is FDA's expectation that patients being treated for COVID-19 with either the EUA-labeled PAXLOVID or NDA-labeled PAXLOVID will receive the same clinical benefit as long as the product is used in accordance with the FDA-approved labeling (Prescribing Information) or authorized labeling (as defined in the LOA), as appropriate.

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[1] https://www.pfizer.com/news/announcements/pfizers-covid-19-oral-antiviral-treatment-transitioning-government-distribution

[2] For more information, please refer to the COVID-19 treatments transition operational guide at: https://aspr.hhs.gov/COVID-19/Therapeutics/Pages/COVID19-Tx-Transition-Guide.aspx

[3] As part of its ongoing assessment of the appropriateness and circumstances of the EUA, FDA will consider the availability of the presentations of Paxlovid that are packaged and labeled in accordance with the approved NDA 217188. See generally section 564(g) of the Federal Food, Drug & Cosmetic Act. See also FDA's guidance titled *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

It's important to note that there are differences in design in carton packaging and the individual blister cards between the EUA-labeled PAXLOVID and NDA-labeled PAXLOVID. To mitigate medication error risks related to EUA-labeled PAXLOVID and NDA-labeled PAXLOVID being simultaneously available, DAV recommends that the Fact Sheet for Health Care Providers and Fact Sheet for Patients, Parents, and Caregivers be revised as described more fully below. In addition, the Sponsor has submitted the following educational documents, which will be made available on Pfizer's website:

- Dosing cards for health care providers and patients, respectively, detailing the differences between the EUA-labeled PAXLOVID and NDA-labeled PAXLOVID.
- A Dear Health Care Provider letter informing health care providers of the differences between the EUA-labeled PAXLOVID and NDA-labeled PAXLOVID.

Updates to Limitations of Authorized Use

DAV recommends that the LOA, Fact Sheet for Health Care Providers, and Fact Sheet for Patients, Parents, and Caregivers be revised to remove the following Limitations of Authorized Use (LOAU):

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

Notably, DAV's recommendation to remove the LOAUs referenced above does not constitute an expansion of the scope of the authorization for the PAXLOVID EUA. The inclusion of the LOAU on the initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 has led to confusion regarding the treatment of mild-to-moderate COVID-19 in patients at high risk for progression to severe COVID-19 who are hospitalized for other reasons. The use of PAXLOVID for treating mild-to-moderate in high risk patients who are hospitalized for reasons other than COVID-19 is within the scope of authorization, so long as the terms and conditions of the EUA are met. FDA is removing this LOAU to reduce confusion on this particular topic.

Moreover, the Fact Sheets continue to detail a 5-day course of PAXLOVID. Per the LOA, the emergency use of PAXLOVID must be in accordance with the authorized Fact Sheets, and therefore the scope of authorization remains the same. Removal of language from the LOAU section regarding use for longer than 5 consecutive days is recommended to achieve editorial alignment with the FDA-approved Prescribing Information (USPI), which does not describe the 5-day course of PAXLOVID as a "Limitation of Use," but does detail a 5-day course in the "Dosage and Administration" section. These clarifying edits reflect FDA's position that while there is no greater safety risk in using PAXLOVID labeled and packaged in accordance with the EUA vs. PAXLOVID labeled and packaged in accordance with the NDA for longer than 5

consecutive days, there is also insufficient data to support a treatment duration longer than 5 consecutive days.

Virology – monitoring of genomic databases, emergence of SARS-CoV-2 variants and susceptibility to nirmatrelvir

Since the initial EUA, Pfizer has been required to monitor genomic databases and report the emergence of SARS-CoV-2 variants with amino acid changes in M^{pro} or M^{pro} cleavage sites, and to conduct additional follow-up assessments as needed to assess variant susceptibility to nirmatrelvir. These conditions are currently described as follows under Conditions L1 and L2:

> 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.

These conditions are the subject of a postmarketing requirement for NDA 217188 (PMR 4392-5). DAV recommends that the LOA be revised to remove the above conditions requiring the collection and analysis of data related to PAXLOVID to avoid unnecessary redundancy.

Summary of Specific Fact Sheet Revisions:

- In the Fact Sheet for Healthcare Providers, the following key revisions are recommended in the highlights and Sections 1 and 16:
  - Removal of the Limitations of Authorized Use regarding use in hospitalized patients and duration of treatment in the highlights and Section 1.
  - Addition of the description of NDA-labeled PAXLOVID to Section 16
- In the Fact Sheet for Patients, Parents, and Caregivers, the following revisions are recommended:

- communicate that two presentations of PAXLOVID, the EUA-labeled PAXLOVID and NDA-labeled PAXLOVID, are now available, and add pictures of the NDA-labeled PAXLOVID

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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