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	September 26, 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	Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}: also referred to as $3CL^{pro}$ 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 M^{pro}. 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 and Other Documents

The PAXLOVID EUA Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents, and Caregivers are being revised at this time for the following reasons:

1. **To Update the Fact Sheet for Healthcare Providers with Information on SARS-CoV-2 Resistance to Nirmatrelvir in Cell Culture.**

   Recent studies conducted by the sponsor and others[1,2] have identified a number of SARS-CoV-2 M^{pro} substitutions and combinations of M^{pro} substitutions associated with nirmatrelvir resistance in cell culture. Most of these substitutions and combinations of substitutions were not previously included in the PAXLOVID EUA Fact Sheet for Healthcare Providers. Therefore, the "Antiviral Resistance" subsection of Section 12.4 is being revised to provide a summary of SARS-CoV-2 M^{pro} substitutions associated with nirmatrelvir resistance in cell culture. The revisions also highlight the fact that the M^{pro} E166V and L50F+E166V substitutions, which have been associated with nirmatrelvir resistance in cell culture, were identified in three participants treated with PAXLOVID in the pivotal clinical trial EPIC-HR, although these participants did not experience hospitalization or death. The clinical significance of these M^{pro} substitutions is unknown.

2. **To Update the Fact Sheet for Healthcare Providers with Information on Nirmatrelvir Activity Against SARS-CoV-2 Omicron Sub-Variants and Activity Against SARS-CoV-2 in Animal Models.**

   Recent studies conducted by the sponsor have demonstrated that nirmatrelvir retains activity against the Omicron sub-variants BA.2, BA.2.12.1, and BA.4 in cell culture. Therefore, the "Antiviral Activity" subsection of Section 12.4 is being revised to indicate these findings. Other studies have found that nirmatrelvir also retains activity against the Omicron sub-variants BA.2.75 and BA.5 in cell culture. Lastly, the "Antiviral Activity Against SARS-CoV-2 in Animal Models" subsection of Section 12.4 is being revised to provide a summary of results from a new animal study conducted by the sponsor, in which the activity of nirmatrelvir, ritonavir, and nirmatrelvir+ritonavir against mouse-adapted SARS-CoV-2 was investigated in mice.

3. **To Update the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients, Parents, and Caregivers to State that Anaphylaxis has been Reported with PAXLOVID.**

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[1] Iketani, S, Mohri, H, Culbertson, B et al., Multiple Pathways for SARS-CoV-2 Resistance to Nirmatrelvir. bioRxiv. 2022Aug18 (Preprint/not yet peer reviewed) available: https://doi.org/10.1101/2022.08.07.499047

[2] Zhou, Y, Gammeltoft, K, Ryberg, L et al. Nirmatrelvir Resistant SARS-CoV-2 Variants with High Fitness In Vitro. bioRxiv. 2022Jun07 (Preprint/not yet peer reviewed) available: https://doi.org/10.1101/2022.06.06.494921

The Fact Sheet for Healthcare Providers currently includes the warning and precaution "Allergic Reactions/Hypersensitivity" which states that hypersensitivity reactions have been reported with PAXLOVID and that cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with ritonavir, a component of PAXLOVID. However, since that warning and precaution was added, there have been 14 post-authorization reports indicative of anaphylaxis after PAXLOVID use (reported in FAERS through August 29, 2022). As such, Sections 5.2, 6.2, and 17 of the Fact Sheet for Healthcare Providers are being revised to indicate that anaphylaxis has been reported with PAXLOVID; other small, editorial changes to the language are also being made. Similar updates about anaphylaxis being reported with PAXLOVID use are being added to the Fact Sheet for Patients, Parents, and Caregivers.

Summary of Fact Sheet Revisions:

- Section 5.2 of the Fact Sheet for Healthcare Providers was renamed Hypersensitivity Reactions and now reads as follows:
    - *Anaphylaxis and other hypersensitivity reactions have been reported with PAXLOVID [see Adverse Reactions (6.2)]. Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of PAXLOVID (refer to NORVIR prescribing information). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.*
    - Similar changes were made to Sections 6.2 and 17 of the Fact Sheet for Healthcare Providers as well as to the Fact Sheet for Patients, Parents, and Caregivers.
- Section 12.4 of the Fact Sheet for Healthcare Providers (Microbiology) was modified as follows:
    - The "Antiviral Activity" subsection was revised to indicate that nirmatrelvir had similar activity against SARS-CoV-2 Omicron sub-variants BA.2, BA.12.1, and BA.4 in cell culture compared to previous SARS-CoV-2 variants.
    - The "Antiviral Activity Against SARS-CoV-2 in Animal Models" subsection was revised to add a summary of the sponsor's new study on the activity of nirmatrelvir, ritonavir, and nirmatrelvir+ritonavir against mouse-adapted SARS-CoV-2 in mice.
    - The "Antiviral Resistance" subsection was divided into two subsections: "Antiviral Resistance in Cell Culture and Biochemical Assays" and "Antiviral Resistance in Clinical Trials." The subsection on resistance in cell culture and biochemical assays was revised and now reads as follows:

SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 8 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 8: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitution (EC_{50} value fold change)	*T21I (1.1-4.6), L50F (1.4-4.2), P108S (ND), T135I (ND), F140L (ND), S144A (2.2-2.5), C160F (ND), E166A (3.3), E166V (25-267), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-2.3), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (2.1-5.5).*
≥2 Substitutions (EC_{50} value fold change)	*T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-163), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).*

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold-change based on K_i values) of nirmatrelvir: G15S (4.4), Y54A (24.0), T135I (3.2), F140A (39.0), F140L (5.4), S144A (92.0), S144E (470), S144T (160), H164N (6.4), E166A (33.0), E166G (16.0), H172Y (230), A173V (26.0), V186G (13.0), Q189K (65.0), Q192L (28.0), Q192P (33.0), and D248E (3.7). The clinical significance of these substitutions is unknown.

- The "Antiviral Resistance in Clinical Trials" subsection was revised by adding the following statement: "In one subject with a baseline M^{pro} L50F substitution, the M^{pro} E166V substitution co-occurred with L50F on Day 5 (included in counts above). The M^{pro} E166V and L50F+E166V substitutions have been associated with nirmatrelvir resistance in cell culture (Table 8)." In addition, the following statements were removed: "In a biochemical assay, the P132H/L/S,

A260V, and A266V M^{pro} substitutions did not reduce nirmatrelvir activity (K_i fold-change ≤1, <1, and ~2, respectively). The potential phenotypic effect on nirmatrelvir susceptibility for the other substitutions is unknown."

- Minor edits were made to the "Viral RNA Rebound" and "Cross-Resistance" subsections.

- Minor edits were made to Section 14.1 of the Fact Sheet for Healthcare Providers (Clinical Studies) for 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/

JONATHAN M RAWSON
09/26/2022 08:37:44 AM

PATRICK R HARRINGTON
09/26/2022 08:40:01 AM

STEPHANIE B TROY
09/26/2022 08:44:57 AM

JULIAN J O REAR
09/26/2022 12:50:40 PM

WENDY W CARTER
09/26/2022 01:31:30 PM