

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) ¹	000105
Date of Memorandum	February 23, 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)
Integrated Review Completion Date for 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)

¹ If a pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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
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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 factsheets are being revised at this time for the following reasons:

1. To add information regarding the post-authorization report of cases of hypersensitivity reactions in association with PAXLOVID use.

The label for Norvir (ritonavir 600 mg po bid used as chronic therapy as a component HIV treatment) contains a Warning and Precaution about allergic reactions that states the following:

- *Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.*

This Warning and Precaution was not included in the PAXLOVID Fact Sheet with the original authorization because no signal for hypersensitivity reactions was seen in the PAXLOVID clinical trials and because it was unclear if hypersensitivity reactions would be seen with the lower ritonavir dose and shorter duration administered as part of PAXLOVID.

However, in late January 2022, DAV was made aware of four FAERS reports regarding clinically significant hypersensitivity reactions during or after PAXLOVID treatment; three additional cases through February 7, 2022, for a total of seven cases, were discovered after subsequent communications with the Sponsor. In addition, fifteen cases were reported describing skin-related symptoms without swelling or shortness of breath that are also possible hypersensitivity reactions. These reports are summarized in Table 1 and Table 2 below.

Table 1. Summary of Reports for Clinically Significant Hypersensitivity Reactions

FAERS #/ Country	Age/Sex	Symptom(s)	Onset	Intervention	Outcome	Concomitant meds reported
20306799 US	67 F	Urticaria, pruritus, facial swelling	After third dose	Discontinued drug	Symptoms subsided after 10+ hours	Yes (no treatment dates)
20334069 US	70 F	Tongue swelling, lip tingling	After first dose (worse after second dose)	Advised to discontinue drug	Unknown	No
20334125 US	66 M	Tongue swelling, sore throat, chest pain, dyspnea, increased BP	After second dose	Discontinued drug	Symptoms resolved	Yes (none recently started)
20347548 US	80 F	Dyspnea, possible laryngeal edema	After first dose	Unknown	Unknown	No
20378409, 20387833 US	72 F	Lip tingling, tongue swelling	First day	Unknown	Unknown	No
Toxic Report* 925 US	56 M	Chest discomfort, dyspnea, nausea	After first dose	Discontinued drug	Symptoms resolved	Yes (no concomitant medications)
20416823, 20432809 US	77 M	Dysphagia, oropharyngeal pain, throat tightness	After second dose	Unknown	Unknown	No

Abbreviations: F, female; M, male.

*This case was not from FAERS but from the ToxIC Registry, a multi-center toxico-surveillance and research network overseen by the American College of Medical Toxicology.

Table 2. Summary of FAERS Reports for Other Rash Adverse Events

FAERS #/ Country	Age/Sex	Symptom(s)	Onset (day of treatment)	Intervention	Outcome
20334070 US	50 M	Blisters on lips and nostrils	2	Discontinued drug	Symptoms resolved
20334126	81	Full body rash	2	Unknown	Unknown

US	M				
20346759, 20359786 US	Unknown	Rash on inside of leg	Unknown	Unknown	Unknown
20391329 US	56 M	Blotching/discoloration under forearm, inner bicep, around thighs/calves	1	Discontinued drug.	Unknown
20391535 US	36 F	Rash and "bumps"	1	Cortisone cream, diphenhydramine advised	Unknown
20407351 US	17 F	Facial rash	1	Discontinued drug, diphenhydramine recommended	Unknown
20405987 US	20 F	Hives on hands	Unknown	Unknown	Unknown
20378790 US	31 F	Facial erythema	1	Unknown	Unknown
20351314 US	38 F	Rash, itching	4	Unknown	Unknown
20430212, 20440887 US	63 F	Rash on knuckles, wrist, elbows, knees and itching	10	Unknown	Unknown
20391154 US	48 F	Erythema of body, itchy	2	Diphenhydramine, prednisone	Unknown
20379637 US	79 F	Itchy skin	5	Unknown	Unknown
20415615, 20416840 US	60 F	Pruritus	1	Discontinued drug, dexamethasone and prednisone ordered	Unknown
20415968 US	69 M	Itching	3	Unknown	Unknown
20363122 US	45 F	Itching	Unknown	Discontinued drug	Unknown

Abbreviations: F, female; M, male.

The review team finds that these cases are suggestive of PAXLOVID-associated hypersensitivity reactions. Most events occurred after the first, second, or third dose, and the few cases with a known outcome reported resolution of symptoms after PAXLOVID was discontinued. Notably, some of the cases in Table 1 were suggestive of anaphylaxis. Therefore, the review team recommends the addition of a Warning and Precaution to the PAXLOVID Fact Sheet for Health Care Providers and that the risk of hypersensitivity reactions be described in the PAXLOVID Fact Sheet for Patients.

There was one additional case (FAERS #20432313), not included in the tables because additional information is pending, in which a patient had a multifocal reaction similar to Stevens-Johnsons involving the mucosa (mouth sores and irritated eyes) and multiples sores on his body (described as “some larger than a golf ball”) that began within 10 days of starting PAXLOVID. As both toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have been reported with ritonavir, the warning and precaution will include that these serious hypersensitivity reactions have been reported with components of PAXLOVID.

2. To revise the drug interactions to remove piroxicam from Contraindications (Section 4) and from Established and Other Potentially Significant Drug Interactions (Table 1 in Section 7.3).

The Sponsor listed piroxicam as a contraindicated drug in the Phase 2/3 clinical trials and in the PAXLOVID Fact Sheet and as a drug with established and other potentially significant drug interactions in the PAXLOVID Fact Sheet. This interaction is based on its inclusion in the Norvir 100mg SmPC [[Norvir 100mg film-coated tablets - Summary of Product Characteristics \(SmPC\) - \(emc\) \(medicines.org.uk\)](#)] which states that concomitant use of ritonavir and piroxicam leads to increased piroxicam plasma concentration and thereby increased risk of serious respiratory depression or hematologic abnormalities or other serious adverse effects.

The review team requested a rationale for the continued inclusion of this interaction in the Fact Sheet. The current piroxicam labeling lists CYP2C9 as the primary enzyme involved in the drug’s metabolism. While ritonavir has the potential to induce CYP2C9, concomitant use with piroxicam would lead to decreased piroxicam plasma levels, not increased piroxicam plasma levels as noted in the Norvir SmPC and the Fact Sheet. Further, the piroxicam labeling does not include a clinical recommendation regarding coadministration with strong CYP3A4 inhibitors such as ritonavir. Thus, the review team recommends deletion of this interaction if a reasonable rationale for its inclusion cannot be provided.

The Sponsor responded that after further review of the Norvir (ritonavir) and Feldene (piroxicam) package inserts, they agree with the deletion of piroxicam from the list of contraindicated drugs because a CYP3A4-based inhibitory interaction is unlikely to occur as piroxicam is mainly metabolized by CYP2C9.

3. To update the reporting requirements for serious adverse events in Sections 6.4 and 6.5 for consistency with other Fact Sheets.

Summary of Fact Sheet Revisions:

- The following Warning and Precaution was added to the Healthcare Provider Fact Sheet:

5.2 Allergic Reactions/Hypersensitivity

Hypersensitivity reactions have been reported with PAXLOVID including urticaria, angioedema, dyspnea, mild skin eruptions, and pruritus. Cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with components of PAXLOVID (refer to NORVIR labeling). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

- Section 6 of the Healthcare Provider Fact Sheet was revised to update the language in Section 6.4 (Required Reporting for Serious Adverse Events and Medication Errors) and to add the following sections:

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions [see Warnings and Precautions (5.2)]

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

- Sections 4 and 7.3 were revised to remove piroxicam from the list of contraindicated medications and from the list of established and other potentially significant drug interactions.

- Section 17 of the Healthcare Provider Fact Sheet (Patient Counseling Information) was also updated to include the following:

Allergic Reactions/Hypersensitivity

Inform patients that hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction [see *Warnings and Precautions (5.2)*].

- The Patient Fact Sheet was updated to include these new hypersensitivity safety events.

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/

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