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	January 31, 2025
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 Nestor Duci - Senior Manager Global Regulatory Affairs 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	Nirmatrelvir 150 mg tablets Ritonavir 100 mg tablets
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)	Pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of 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 EUA Fact Sheet for Healthcare Providers is recommended to be revised at this time for the following reasons:

The labeling for the PAXLOVID U.S. Prescribing Information (USPI) for the approved NDA 217188 (PAXLOVID USPI) is being updated to include information regarding dosing PAXLOVID in patients with severe renal impairment based on the results of the Phase 1, open-label, single-arm, non-randomized trial in outpatient subjects with COVID-19 and severe renal impairment, EPIC-SRI (C4671028). Previously, dosing of PAXLOVID was limited to patients with an estimated glomerular filtration rate (eGFR) of greater than 30 mL/min. The pharmacokinetic (PK) and safety data from EPIC-SRI support the following dose of PAXLOVID in patients with severe renal impairment (eGFR <30 mL/min), including those on intermittent hemodialysis:

- Day 1: 300 mg nirmatrelvir (two 150 mg nirmatrelvir tablets)/100 mg ritonavir (one ritonavir 100 mg tablet) once
- Days 2-5: 150 mg nirmatrelvir (one 150mg tablet) with 100 mg ritonavir (one 100 mg tablet) once daily

The overall safety profile in EPIC-SRI is consistent with the known safety profile of PAXLOVID as observed from subjects in Phase 2/3 clinical trials. The administration of nirmatrelvir 300 mg/ritonavir 100 mg once on Day 1 followed by nirmatrelvir 150 mg/ritonavir 100 mg once daily on Days 2-5 in subjects with severe renal impairment, either requiring hemodialysis or not requiring hemodialysis resulted in comparable exposures on Day 1 and at steady-state compared to those observed in subjects with normal renal function receiving nirmatrelvir 300 mg/ritonavir 100 mg twice daily for 5 days.

Additionally, minor changes were recommended in the microbiology section of the label (Section 12.4) based on updated nonclinical virology studies.

The EUA Fact Sheet for Healthcare Providers is being updated to conform with the changes being made to the PAXLOVID USPI.

As published in the Recommended Acceptable Intake Limits (RAIL) for Nitrosamine Drug Substance-Related Impurities Guidance [1], a component of PAXLOVID, ritonavir, may contain a nitrosamine, (b) (4) . Using the Carcinogenic Potency Categorization Approach, FDA placed this impurity in potency category (b) (4) which has a recommended acceptable intake (AI) limit of (b) (4) ng/day. The recommended AI limit is calculated based on the daily exposure to a compound, such as a nitrosamine impurity, that approximates 1:100,000 cancer risk after a lifetime (70 years) of daily exposure. The Applicant estimated that ritonavir in the formulation of PAXLOVID at the

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits; updated January 17, 2025

approved dosing regimen in individuals without severe renal impairment has an (b) (4) level between (b) (4) ng/day with a dose of 200 mg/day. The proposed ritonavir dose for this EUA revision in adolescents 12 years of age and older weighing at least 40kg with severe renal impairment is 100 mg/day.

Given that severe renal impairment is considered to be a significant risk factor for progression to severe COVID-19, and there are no approved oral options to treat mild-to-moderate COVID-19 in adolescents 12 years of age and older weighing at least 40kg with severe renal impairment, and the recommended PAXLOVID 5- day dosing regimen in this population contains half the daily dosage of ritonavir in the PAXLOVID regimen authorized for use in adolescents 12 years of age and older weighing at least 40 kg without severe renal impairment, the benefit-risk of PAXLOVID remains favorable in the adolescents 12 years of age and older weighing at least 40kg with severe renal impairment population while the Applicant continues to address this issue.

Summary of Revisions:

In the Fact Sheet for Healthcare Providers the following key revisions are recommended:

- Updating Section 2, Dosage and Administration, to include the following dosage recommendations for patients with severe renal impairment, including those on hemodialysis:
    - Day 1: 300 mg nirmatrelvir (two 150 mg nirmatrelvir tablets)/100 mg ritonavir (one ritonavir 100 mg tablet) once.
    - Days 2-5: 150 mg nirmatrelvir (one 150mg tablet) with 100 mg ritonavir (one 100 mg tablet) once daily.

- Update Section 6.1, Clinical Trials Experience, to include data from EPIC-SRI.
- Update Section 8.6, Renal Impairment to include dosing for severe renal impairment.
- Update Section 12, Clinical Pharmacology, to include population pharmacokinetic and clinical pharmacokinetic data that support expanding the indication to encompass patients with severe renal insufficiency.
    - Update Section 12.4, Microbiology, to reflect updated nonclinical virology studies.

Patient Eligibility Screening Checklist and Drug Interaction Tool was updated to include dosing in patients with severe renal impairment.

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.

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/s/

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