



December 22, 2021

****Emergency Use Authorization****

Nirmatrelvir and Ritonavir (Paxlovid®) for Treatment of COVID-19

Mechanism of action^{1,2}:

Nirmatrelvir and ritonavir, the active components of Paxlovid®, are oral antiviral agents. Nirmatrelvir is a SARS-CoV-2 main protease inhibitor which stops the virus from replicating. Ritonavir is an HIV-1 protease and CYP3A inhibitor, which has no activity against SARS-CoV-2 on its own but which slows the CYP3A-mediated metabolism of nirmatrelvir to help it remain in the body for a longer period at higher concentrations. Paxlovid® is an investigational drug and is not approved for any uses, including use for the treatment of coronavirus disease (COVID-19).

Current Status & Indications^{1,2}:

On December 22, 2021, the U.S. Food and Drug Administration issued an [emergency use authorization](#) (EUA) for Paxlovid® (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and [who are at high risk for progression to severe COVID-19](#), including hospitalization and death.

Availability¹:

Distribution of the authorized Paxlovid® will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply Paxlovid® to authorized distributor(s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed. The IHS National Supply Service Center anticipates that ordering will be available for IHS facilities in a limited capacity during the month of January 2022.

Limitations of Authorized Use³:

Paxlovid® is not authorized for use;

- In individuals requiring hospitalization due to severe or critical COVID-19.
- As pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
- For duration longer than 5 consecutive days.

Efficacy and Safety^{2,3}:

The primary data supporting this EUA are from the [EPIC-HR Trial](#), a phase 2/3 randomized, double-blind, placebo-controlled clinical trial in adults aged 18 years and older with confirmed SARS-CoV-2 infection within 5 days prior to randomization and at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19.

The main outcome in the trial was the proportion of participants with COVID-19 related hospitalization or death from any cause after receiving Paxlovid® or placebo within five days of symptom onset. In this trial, 1,039 people received Paxlovid® and 1,046 received a placebo. In the primary analysis, Paxlovid® recipients saw an 88% reduced risk of hospitalization and death within 5 days of symptom onset compared to those with placebo, a statistically significant difference.

Possible side effects of Paxlovid® include: dysgeusia, diarrhea, hypertension, and myalgia. The proportions of subjects who discontinued treatment due to an adverse event were 2% in the Paxlovid® group and 4% in the placebo group.

Dosage and Administration^{2,3}:

The dosage for Paxlovid® is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within Paxlovid®.* Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

The 5-day treatment course of Paxlovid® should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid®, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

Warnings and Precautions³:

- **Serious Adverse Reactions Due to Drug Reactions:** Initiation of Paxlovid®, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving Paxlovid®, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid®, respectively.
- **Hepatotoxicity:** Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid® to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.
- **Risk of HIV-1 Resistance Development:** Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Current EUA Fact Sheets for Paxlovid®:

- ❖ (1) [Healthcare Providers](#)
- ❖ (2) [Patients, Parents, and Caregivers](#)

Required Reporting for Serious Adverse Events and Medication Errors under the EUA³:

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to Paxlovid® within 7 calendar days from the healthcare provider's awareness of the event. The FDA recommends that reports, using FDA Form 3500, include:

- Patient demographics and baseline characteristics (patient identifier, age or DOB, gender, weight, ethnicity, and race)
- A statement "Paxlovid® use for COVID-19 under Emergency Use Authorization (EUA)" under the "Describe Event, Problem, or Product Use/Medication Error" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event reports to **FDA MedWatch** using one of the following methods:

1. Complete and submit the report online: www.fda.gov/medwatch/report.htm or
2. Complete and submit a postage-paid FDA Form 3500: www.fda.gov/media/76299/download

*****Federal, Tribal, and Urban programs are all encouraged to put "IHS" into field #26 of the reporting forms.*****

References:

1. Food and Drug Administration. Pfizer Paxlovid® [Letter of Authorization](#). Published December 22, 2021.
2. Food and Drug Administration. FDA News Release. [FDA Authorizes First Oral Antiviral for Treatment of COVID-19](#). Published online Dec 22, 2021.
3. Food and Drug Administration. Paxlovid® (nirmatrelvir and ritonavir): [Fact Sheet for Healthcare Providers](#). December 22, 2021.
4. Food and Drug Administration. Paxlovid® (nirmatrelvir and ritonavir): [Fact Sheet for Patients, Parents, and Caregivers](#). December 22, 2021.