

Purpose of This Document

The purpose of this Safety Reference Sheet is to provide information to clinicians regarding warnings and potential risks associated with use of Paxlovid such as contraindications, precautions, adverse effects (ADRs), and significant drug-drug interactions (DDIs).

Important Note

The content referenced in this Safety Reference Sheet is based on information available at the time of publishing (12/22/2021). For most recent guidance and updates regarding Paxlovid, please refer to the US Food and Drug Administration (FDA) at <https://www.fda.gov/drugs>, and/or Pfizer at <https://www.pfizer.com/news/press-releases>.

Introduction

The FDA granted Emergency Use Authorization (EUA) for nirmatrelvir and ritonavir (Paxlovid) on 12/22/2021. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor to prevent viral RNA replication, and ritonavir (HIV-1 protease inhibitor and CYP3A inhibitor) helps slow the metabolism of nirmatrelvir (a CYP3A4 substrate). Below is a summary of important points from the Paxlovid EUA.

Indication of Paxlovid:

- Treatment of mild-to-moderate COVID-19 in non-hospitalized adults and pediatric patients (12 years of age and older weighing at least 40 kg):
 - with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death
 - having at least one risk factor for progression to severe disease
 - Diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or 60 years of age and older regardless of comorbidities
 - with symptom onset ≤5 days

Limitations of Authorized Use:

- Not authorized for treatment in patients requiring hospitalization due to severe or critical COVID-19
- Not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg
- Not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19
- Not authorized for use for longer than 5 consecutive days

Dosage, Administration and Other Important Points:

- Paxlovid is administered orally at a dose of 300 mg (two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir given twice-daily with or without food for 5 days
- Paxlovid must be started as soon as possible after diagnosis of COVID-19 and within 5 days of symptoms onset
- Dose in moderate renal impairment (eGFR ≥30 to <60 ml/min): reduce regular dose to 150 mg of nirmatrelvir (one 150 mg tablet) with 100 mg of ritonavir (one 100 mg tablet) taken together twice daily for 5 days
- If the patient misses the dose of Paxlovid within 8 hrs of the time it is usually taken then the patient should take it as soon as possible and resume the normal dosing schedule
- If the patient misses a dose by more than 8 hours then the patient should not take the missed dose and instead take the next dose at the regularly scheduled time; the patient should not double the dose to make up for a missed dose
- Paxlovid is not recommended in patients with severe renal impairment with eGFR <30 ml/min
- Paxlovid is not recommended in patients with severe hepatic impairment (Child-Pugh Class C)

- No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat
- Patients on HIV or HCV regimens containing ritonavir- or cobicistat should continue their treatment as indicated

Contraindications

Paxlovid is contraindicated in patients with a history of clinically significant hypersensitivity reactions to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

Table of drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations may lead to serious and/or life-threatening reactions, and thus, are contraindicated with Paxlovid per the EUA (this is not a comprehensive list of all possible drugs that may interact with Paxlovid):

Alpha 1 adrenoreceptor antagonists: alfuzosin	Antipsychotics: lurasidone, pimozide, clozapine
Analgesics: pethidine, piroxicam, propoxyphene	Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
Antianginals: ranolazine	PDE5 inhibitors: sildenafil (Revatio®) when used for PAH
Antiarrhythmics: amiodarone, dronedarone, flecainide, propafenone, quinidine	Sedative/hypnotics: triazolam, oral midazolam
Anti-gout: colchicine	Statins: lovastatin, simvastatin

The following medications are potent CYP3A inducers that are contraindicated with Paxlovid and Paxlovid should not be started immediately after their discontinuation due to the delayed offset of this inducer:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

Warnings and Precautions

A) Risk of Serious Adverse Reactions Due to Drug Interactions

- The plasma concentration of medications metabolized by CYP3A may be increased with Paxlovid, a CYP3A inhibitor
- Medications that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid, respectively
 - These interactions may lead to adverse reactions from greater exposure to Paxlovid, or loss of therapeutic effect of Paxlovid and possible development of viral resistance
- Please refer to table 1 in the [Paxlovid EUA](#) for clinically significant adverse reactions, including contraindicated drugs

B) Hepatotoxicity

- Ritonavir is known to cause transaminase elevations, clinical hepatitis, and jaundice; thus, caution is warranted with the use of Paxlovid in patients with pre-existing liver disease

C) Risk of HIV-1 Resistance Development

- Patients taking Paxlovid may be at risk of developing resistance to HIV protease inhibitors in patients with uncontrolled or undiagnosed HIV-1.

Adverse Reactions

Per the EPIC-HR trial, most common adverse events reported in patients receiving Paxlovid versus placebo:

	Paxlovid, N= 1,109	Placebo, N = 1,115
Altered taste	6%	<1%
Diarrhea	3%	2%

Hypertension	1%	<1%
Myalgia	1%	<1%

Drug-Drug Interactions

Please see the above sections: “Contraindications,” and “Warnings and Precautions” for important guidance regarding drug-drug interactions.

Use in Specific Populations

- A) Pregnancy Risk Summary
 - a. No human data currently available for nirmatrelvir... and published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage.
- B) Lactation
 - a. It is unknown if nirmatrelvir is present in human or animal milk. The effects on the breastfed infant, or the effects on milk production are also unknown for nirmatrelvir and ritonavir.
- C) Contraception
 - a. Use of ritonavir may reduce the efficacy of combined hormonal contraceptives (ethinyl estradiol)
 - b. Patients should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception
- D) Renal and Hepatic Impairment: please refer to the “Introduction” section under “Dosage and Administration.”

Reporting

Report adverse events to FDA MedWatch

<https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program>

References

- 1) Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. 12/22/2021.
<https://www.fda.gov/media/155050/download>