# PAXLOVID™
# (nirmatrelvir tablets; ritonavir tablets)
# Dosing Information Guide

Current as of December 22, 2021.

PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in 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.

The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

## Authorized Use

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in 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.

## Limitations of Authorized Use

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
- PAXLOVID is not authorized for use as preexposure or postexposure prophylaxis for prevention of COVID-19
- PAXLOVID is not authorized for use for longer than 5 consecutive days

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (ie, anti-infectives)

PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under 564(b)(1) of the Food Drug and Cosmetic Act unless the authorization is terminated or revoked sooner.

To view the Fact Sheet for Healthcare Providers, Letter to Healthcare Providers (Dec. 2021), Pharmacist Instruction Sheet, full product information, and other downloadable resources, please visit https://www.covid19oralrx-hcp.com.

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

## IMPORTANT SAFETY INFORMATION

PAXLOVID is **contraindicated in patients with a history of clinically significant hypersensitivity reactions** (eg, toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is **contraindicated with drugs that are highly dependent on CYP3A** for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions: $Alpha_1$-adrenoreceptor antagonist: alfuzosin; Analgesics: pethidine, piroxicam, propoxyphene; Antianginal: ranolazine; Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine; Anti-gout: colchicine; Antipsychotics: lurasidone, pimozide, clozapine; Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine; HMG-CoA reductase inhibitors: lovastatin, simvastatin; PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension; Sedative/hypnotics: triazolam, oral midazolam.

**Please see additional Important Safety Information throughout.**

PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets)
**Dosing Information Guide**

## Discuss Early Treatment & Consider Contraindications and Drug Interactions

### Discuss Early Treatment

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 for the treatment of mild-to-moderate COVID-19 in 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.

- For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)
- Healthcare providers should consider the benefit-risk for an individual patient

### Consider Contraindications and Drug Interactions

The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult Section 4: Contraindications, Section 5.1: Risk of Serious Adverse Reactions Due to Drug Interactions, and Section 7: Drug Interactions of the Fact Sheet for Healthcare Providers prior to prescribing and during treatment for potential drug interactions.

PAXLOVID is contraindicated in/with:

- Patients with a history of clinically significant hypersensitivity reactions (eg, toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product

(Continued on next page)

**Download the Fact Sheet for Healthcare Providers**
https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**
https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

### IMPORTANT SAFETY INFORMATION

PAXLOVID is **contraindicated with drugs that are potent CYP3A inducers** where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

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

There are limited clinical data available for PAXLOVID. **Serious and unexpected adverse events may occur** that have not been previously reported with PAXLOVID use.

**Please see additional Important Safety Information throughout.**

(Continued from previous page)

- Drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:
    - Alpha$_1$-adrenoreceptor antagonist: alfuzosin
    - Analgesics: pethidine, piroxicam, propoxyphene
    - Antianginal: ranolazine
    - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
    - Antigout: colchicine
    - Antipsychotics: lurasidone, pimozide, clozapine
    - Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
    - HMG-CoA reductase inhibitors: lovastatin, simvastatin
    - PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
    - Sedative/hypnotics: triazolam, oral midazolam
- Drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:
    - Anticancer drugs: apalutamide
    - Anticonvulsant: carbamazepine, phenobarbital, phenytoin
    - Antimycobacterials: rifampin
    - Herbal products: St. John's Wort (*hypericum perforatum*)

Drug Interactions:

- Initiation of PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), 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. These interactions may lead to:
    - Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
    - Clinically significant adverse reactions from greater exposures of PAXLOVID
    - Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

See Table 1 in Section 7: Drug Interactions of the Fact Sheet for Healthcare Providers for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

## IMPORTANT SAFETY INFORMATION

**Risk of Serious Adverse Reactions Due to Drug Interactions**: 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. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
- Clinically significant adverse reactions from greater exposures of PAXLOVID
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

Consult Table 1 of the Fact Sheet for Healthcare Providers for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

**Please see additional Important Safety Information throughout.**

## Oral Treatment Regimen: How to Take

The dosage for emergency use of PAXLOVID authorized under EUA is 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet) with all 3 tablets taken together orally twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.

### How Do Patients Take PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets)?

- PAXLOVID consists of 2 medicines: nirmatrelvir and ritonavir. Patients should take 2 tablets of nirmatrelvir (150 mg) with 1 tablet of ritonavir (100 mg) by mouth twice daily (in the morning and in the evening) for 5 days. For each dose, all 3 tablets should be taken at the same time
- PAXLOVID can be taken with or without food
- Patients should swallow the tablets whole. They should not chew, break, or crush the tablets
- Alert the patient of the importance of completing the full 5-day treatment course and of continued isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2

### Dose Adjustments

- Renal Impairment: No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined. Healthcare providers should counsel patients about renal dosing instructions
- Hepatic Impairment: No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment
- Important Drug Interactions with PAXLOVID: No dosage adjustment is required when coadministered with other products containing ritonavir or cobicistat. Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated

Refer to other sections of the Fact Sheet for Healthcare Providers for important drug interactions with PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

### IMPORTANT SAFETY INFORMATION

**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.**

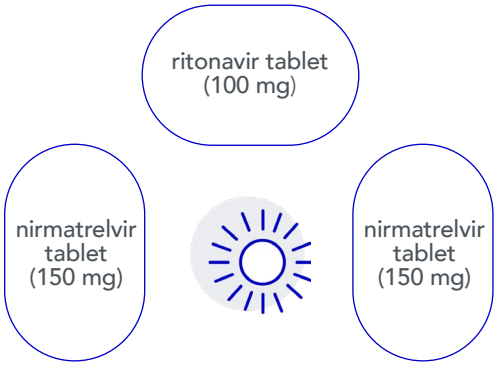
**Adverse events** in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

**Please see additional Important Safety Information throughout.**

## Set a Treatment Schedule

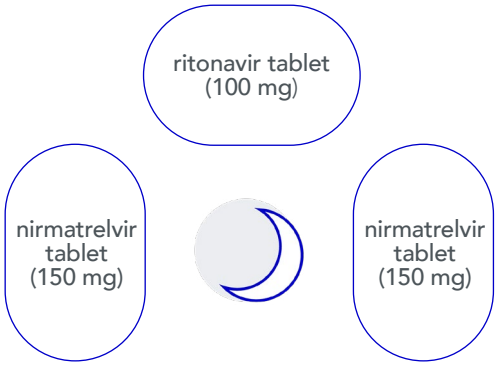
**Patients should complete the entire 5-day treatment course as prescribed, which consists of:**

### Morning Dose




Take 3 tablets at the same time.

### Evening Dose




Take 3 tablets at the same time.

NOTE: To ensure appropriate dosing in patients with moderate renal impairment, reduce the dosage of PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Healthcare providers should counsel patients about renal dosing instructions.

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

## IMPORTANT SAFETY INFORMATION

**Required Reporting for Serious Adverse Events and Medication Errors:** The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event.

Submit adverse event and medication error reports to FDA MedWatch using one of the following methods:
- Online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 and returning by mail/fax
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to: www.pfizersafetyreporting.com, or by fax (1-866-635-8337) or phone (1-800-438-1985).

**Please see additional Important Safety Information throughout.**

## Emphasize the Need for Treatment Adherence

Educate patients on the importance of adhering to their prescribed PAXLOVID treatment course correctly and in its entirety. If patients experience side effects while taking PAXLOVID, they should speak with the prescribing healthcare provider before discontinuing treatment.

### If patients do not properly adhere to the prescribed dosing and administration of PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), take the following measures:

- Missed Dose: If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, advise the patient to take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, tell them to not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose
- Overdose: Advise your patient to call the prescribing healthcare provider or go to the nearest emergency room right away. Treatment of overdose with PAXLOVID should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

### IMPORTANT SAFETY INFORMATION

**PAXLOVID is an inhibitor of CYP3A** and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CPY3A substrates may require a dose adjustment or additional monitoring.

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

**Please see additional Important Safety Information throughout.**

**Find Additional Information**
about PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), including the Fact Sheet for Healthcare Providers, at https://www.covid19oralrx-hcp.com/.

### Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event, using FDA Form 3500 (for information on how to access this form, see below).

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787
  - Fax to 1-800-FDA-0178
- Call 1-800-FDA-1088 to request a reporting form

### In addition, please provide a copy of all FDA MedWatch forms to:

| Website | Fax number | Telephone number |
|---|---|---|
| www.pfizersafetyreporting.com | 1-866-635-8337 | 1-800-438-1985 |

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with PAXLOVID.

For information on what the FDA recommends to include in your Form 3500 submission, please refer to Section 6.4: Required Reporting for Serious Adverse Events and Medication Errors in the Fact Sheet for Healthcare Providers here.

For more information

**Contact One of the Following Groups**
For **Medical Information** visit www.pfizermedicalinformation.com or call 1-800-438-1985

For **General Product Inquiries** call 1-877-C19PACK (1-877-219-7225)

## IMPORTANT SAFETY INFORMATION

**Pregnancy:** There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

**Please see additional Important Safety Information throughout.**

**Download the Fact Sheet for Healthcare Providers**
https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**
https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

**Download the Pharmacist Instruction Sheet**
https://www.covid19oralrx-hcp.com/resources

**Download the Letter to Healthcare Providers (Dec. 2021)**
https://www.covid19oralrx-hcp.com/resources

## IMPORTANT SAFETY INFORMATION

**Lactation:** There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

**Contraception:** Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

**Pediatrics:** PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR.

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment. No dosage adjustment is needed in patients with mild renal impairment. **In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID** to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Providers should counsel patients about renal dosing instructions. **PAXLOVID is not recommended in patients with severe renal impairment** (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, **PAXLOVID is not recommended for use in patients with severe hepatic impairment**.

**Reference:** PAXLOVID Fact Sheet for Healthcare Providers. Pfizer Inc.; December 22, 2021.

**Please see Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents, and Caregivers.**

**Download the Fact Sheet for Healthcare Providers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_HCP.pdf

**Download the Fact Sheet for Patients, Parents, and Caregivers**

https://www.covid19oralrx-hcp.com/files/Fact_Sheet_Patient.pdf

**Download the Pharmacist Instruction Sheet**

https://www.covid19oralrx-hcp.com/resources

**Download the Letter to Healthcare Providers (Dec. 2021)**

https://www.covid19oralrx-hcp.com/resources