COVID-19 Oral Antiviral Treatment

Considerations for therapy and the pharmacist's role

FDA authorized 2 oral antiviral COVID-19 therapeutics under emergency use authorizations (EUAs). These therapies are indicated for treatment of mild to moderate COVID-19 in individuals at high risk for progression to severe COVID-19 following a positive COVID-19 test. They should be initiated within 5 days of symptom onset. These treatments are not authorized for preexposure or postexposure prevention of COVID-19.

Paxlovid consists of nirmatrelvir, a SARS-CoV-2 main protease inhibitor which prohibits viral replication, and ritonavir, an HIV-1 protease inhibitor/CYP3A4 inhibitor which slows the breakdown of nirmatrelvir.

Molnupiravir works by inhibiting viral reproduction by increasing mutations in the SARS-CoV-2 virus' genetic code that prevent it from replicating further.

Pharmacists have a critical role in the safe dispensation of these products because they require enhanced attention to safety considerations, patient education, handling, and reporting. However, per FDA's guidance, pharmacists are **not eligible** to order or prescribe Paxlovid or molnupiravir at this time. These medications may only be prescribed by specific health care providers who are authorized to prescribe drugs in this therapeutic class. However, pharmacists can generate awareness, answer patient questions, and/or assess patients for eligibility following a confirmed COVID-19 infection and refer patients to their provider for a prescription.

FDA-authorized oral antiviral COVID-19 therapeutics

Therapy	Paxlovid	Molnupiravir
Manufacturer	Pfizer	Merck
Authorized use	Treatment of mild to moderate COVID-19 in individuals at high risk for progression to severe COVID-19	Treatment of mild-to-moderate COVID-19 disease in in individuals at high risk for progression to severe COVID-19 disease *Note: Molnupiravir should only be administered to patients for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.*
Age restrictions	Must be 12 years or older and weigh 40 kg or more	Must be 18 years or older
Initiation of therapy	Within 5 days of symptom onset	

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Therapy	Paxlovid	Molnupiravir
Dosing and administration	**Normal renal function/mild impairment (eGFR ≥60 to <90 mL/min):** 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet). All 3 tablets taken together twice daily for 5 days. **Moderate Renal Impairment (eGFR 30-60 mL/min):** 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet). Both tablets taken together twice daily for 5 days. **Avoid in severe renal impairment (eGFR below 30 mL/min)** **Avoid in severe hepatic impairment (Child-Pugh Class C)**	800 mg (four 200 mg capsules) taken twice daily for 5 days
Contraindications	• History of clinically significant hypersensitivity reactions to any of the active or inactive components • Coadministration with drugs highly dependent upon CYP3A for clearance and for which elevated concentrations are associated with serious reactions • Coadministration with potent CYP3A inducers	No contraindications have been identified based upon limited available data.
Additional considerations	Completion of the full 5 consecutive day treatment course and continued isolation in accordance with the most recent public health recommendations are essential to maximize viral clearance and minimize transmission of SARS-CoV-2.	
More information	• Fact sheet for health care providers • Fact sheet for patients, parents, and caregivers • Frequently asked questions • ISMP medication safety issues with Paxlovid	• Fact Sheet for Health Care Providers • Fact Sheet for Patients, Parents, and Caregivers • Frequently asked questions

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Paxlovid

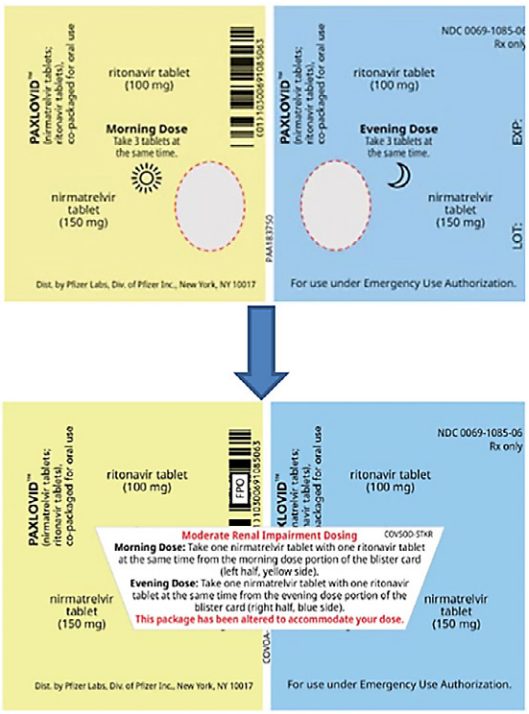
How is Paxlovid supplied?

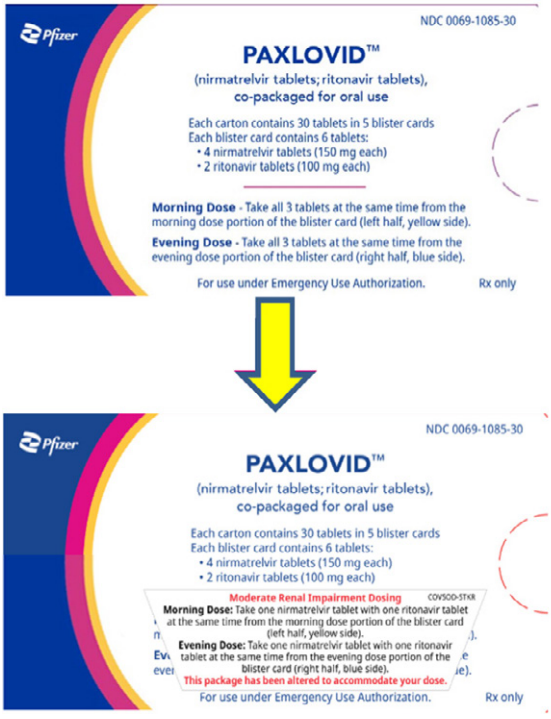
Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Prescriptions should specify the numeric dose of each active ingredient within Paxlovid. It is supplied as 5 daily dose blister cards, with each dose consisting of two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet. Each blister card contains a daily morning dose of 3 tablets and evening dose of 3 tablets. This medication should be stored at room temperature.

How should Paxlovid be taken?

Each dose of Paxlovid contains 300 mg of nirmatrelvir and 100 mg of ritonavir and is administered as 3 tablets: two pink 150 mg nirmatrelvir tablets and one white 100 mg ritonavir tablet. Pharmacists should instruct patients with normal or mildly impaired renal function (eGFR ≥60 to <90 mL/min) to take 2 pink tablets of nirmatrelvir with one white tablet of ritonavir by mouth for a total of 3 tablets twice daily for 5 days.

For patients with moderate renal impairment (eGFR ≥30 to < 60 mL/min), a dose reduction is needed. The reduced dose prescribed should be 150 mg of nirmatrelvir and 100 mg of ritonavir twice daily for 5 days. Therefore, pharmacists should remove one of the nirmatrelvir tablets for both the morning and evening doses from each blister card before dispensing Paxlovid. Pharmacists should then cover the empty blisters on all 5 cards with manufacture-supplied stickers. To receive preprinted stickers with dosing instructions for your pharmacy, contact c19therapies@amerisourcebergen.com via email. The images below demonstrate how the stickers should be used when a dose adjustment is made.





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Instruct patients to take all tablets together for each dose with or without food, and to not chew, break, or crush them. If a patient misses a dose of Paxlovid, it is safe for the patient to take the medication as soon as possible within 8 hours of the time it is usually taken and resume their normal dosing schedule.

What are the possible side effects of Paxlovid?

- **Hepatoxicity:** Pharmacists should educate patients about the signs and symptoms of hepatotoxicity, including dark-colored urine, pale colored stools, itchy skin, and abdominal pain.
- **Risk for HIV-1 drug resistance development:** The ritonavir in Paxlovid may increase the risk of developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.
- **Other common adverse reactions:** These include altered sense of tase, diarrhea, high blood pressure, and muscle aches.

Does Paxlovid have contraindications for use?

Paxlovid is a CYP3A inhibitor and is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. Pharmacists should refer to the Paxlovid's Fact sheet for healthcare providers for a complete list of serious drug interactions.

What are the warnings and precautions associated with Paxlovid beyond hepatoxicity and HIV-1 drug resistance development risk?

Exercise caution when initiating or discontinuing other medications, as Paxlovid contains ritonavir, a CYP3A inhibitor which may cause change in plasma concentrations of drugs primarily metabolized by CYP3A. Pharmacists should always 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.

Is Paxlovid safe to take during pregnancy?

There is currently no experience treating pregnant or breastfeeding individuals with Paxlovid; however, the benefit of treatment may be greater than the risk. Effective barrier contraception or avoiding sexual activity is recommended while taking Paxlovid. Patients who are pregnant and/or breastfeeding should discuss their options with their health care provider.

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Molnupiravir

How is molnupiravir supplied?

Molnupiravir is supplied as 200 mg capsules in 40-count bottles (5-day supply) and should be stored at room temperature.

How should molnupiravir be taken?

Molnupiravir is administered as four 200 mg capsules (800 mg total), which are taken orally every 12 hours for 5 days with or without food. They should not be opened, broken, or crushed. If a patient misses a dose of molnupiravir, it is safe for the patient to take the medication as soon as possible within 10 hours of the time it is usually taken and resume their normal dosing schedule.

Molnupiravir should only be administered to patients for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

What are the possible side effects of molnupiravir?

- **Bone and cartilage toxicity:** Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.
- **Other common adverse reactions** include diarrhea, nausea, and dizziness.

Is molnupiravir safe to take during pregnancy?

Molnupiravir is **not recommended** for use during pregnancy. Based on findings from animal studies, molnupiravir may cause fetal harm when administered to pregnant individuals. Molnupiravir is authorized to be prescribed to a pregnant individual only after the health care provider has determined that the benefits of treatment would outweigh the risks.

Pharmacists should advise individuals of childbearing potential to use effective methods of contraception during treatment with molnupiravir and for 4 days after their last dose. In individuals who may become pregnant, pharmacists should recommend consistent use of reliable contraception consistently and correctly during treatment with molnupiravir and for 4 days after their last dose.

Mandated adverse events reporting

It is mandatory for providers to report all serious adverse events or medication errors related to a medication available under an EUA via the FDA MedWatch reporting program or by calling 1-800-FDA-1088.

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Reimbursement

Since these products are distributed at no cost, there will not be payment for the product; however, CMS has recommended plans offer an enhanced dispensing fee for the additional services and precautions required to dispense these products.

Pharmacies dispensing these medications will need to consider how to safely dispense these products to individuals who are COVID-19 positive. There will also be time involved in counseling patients regarding how to safely and accurately use these medications.

Based on guidance from the National Council for Prescription Drug Programs (NCPDP), prescription claims can be filled out using the following information to claim the enhanced dispensing fee.

- **NDC for the vaccine product**
- **Quantity dispensed:** Quantity of product dispensed (may need to account for changes due to renal dosing)
- **Days supply:** Number of days prescription will last
- **Professional service code:** "PE"–Patient Education should be submitted to identify the professional services associated with the unique dispensing requirements of the product
- **Ingredient cost:** $0.00 (some payers may require $0.01 to be entered)
- **Basis of cost:** 15 (no cost)
- **Dispensing fee submitted:** Submitted when the pharmacy is seeking reimbursement for the agreed upon dispensing fee of the free product
- **Incentive amount submitted:** Submitted when there are professional service charges associated with the unique dispensing requirements
- **Gross amount due:** Represents the sum of the component fields

Reimbursement will vary. The oral antivirals should be covered by the patient's insurance and should be at no cost to the patient. If a patient is uninsured, pharmacies can submit claims to the Health Resources & Services Administration's Uninsured program. For more information on this program, review "HRSA COVID-19 Uninsured Program and Coverage Assistance Fund" in APhA's Know the Facts: COVID-19 Resources library.