COVID-19 Oral Antiviral Treatment

Considerations for therapy

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. Pharmacists should refer to the National Institutes of Health (NIH) guidelines for the Therapeutic Management of Nonhospitalized Adults with COVID-19 for more information.

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.

As medication stewards, pharmacists have a critical role in the appropriate use of these products because they require enhanced attention to safety considerations, patient education, handling, and reporting.

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
Place in therapy	**Preferred therapy** for the treatment of COVID-19 in outpatient settings	**Alternative therapy** for the treatment of COVID-19 in outpatient settings For use *ONLY* when neither ritonavir-boosted nirmatrelvir (Paxlovid) or remdesivir are available, feasible to use, 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	

COVID-19 Oral Antiviral Treatment (continued)

Considerations for therapy

Therapy	Paxlovid	Molnupiravir
Dosing and administration	**Normal Renal Function to Moderate Renal Impairment (eGFR > 60 mL/min)** 300 mg nirmatrelvir (two 150 mg tablets)/100 mg ritonavir (one 100 mg tablet) taken by mouth together twice daily for 5 days **Moderate Renal Impairment (eGFR ≥30 to <60 mL/min)** 150 mg nirmatrelvir (one 150 mg tablet)/100 mg ritonavir (one 100 mg tablet) taken by mouth 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 molnupiravir (four 200 mg capsules) taken by mouth 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

COVID-19 Oral Antiviral Treatment (continued)

Considerations for therapy

Paxlovid

How is Paxlovid supplied and how should it be taken?

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Prescriptions should specify the numeric dose of each active ingredient within Paxlovid. Paxlovid is supplied in two different Dose Packs outlined below. Each dose pack includes 5 daily blister cards, consisting of a morning and evening dose. Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Dose Pack	Content
Paxlovid nirmatrelvir **300 mg** / ritonavir 100 mg	**Each carton contains:** 30 tablets divided in 5 daily-dose blister cards
	Each blister card contains: 4 pink nirmatrelvir tablets (150 mg each) and 2 white to off-white ritonavir tablets (100 mg each)
	Dosing: patients should be instructed to take 2 nirmatrelvir (150mg) tablets and 1 ritonavir (100mg) tablet **twice daily** for 5 days
Paxlovid nirmatrelvir **150 mg** / ritonavir 100 mg	**Each carton contains:** 20 tablets divided in 5 daily-dose blister cards
	Each daily blister card contains: 2 pink nirmatrelvir tablets (150 mg each) and 2 white to off-white ritonavir (100 mg each)
	Dosing: patients should be instructed to take 1 nirmatrelvir (150mg) tablet and 1 ritonavir (100mg) tablet **twice daily** for 5 days

Special Considerations:

If the dose pack containing 150mg nirmatrelvir/100mg ritonavir is not available, pharmacists dispensing Paxlovid to patients with moderate renal impairment can adjust the packaging for the standard dose pack containing 300mg nirmatrelvir/100mg ritonavir. 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 manufacturer-supplied stickers. To receive preprinted stickers with dosing instructions for your pharmacy, contact c19therapies@amerisourcebergen.com via email.

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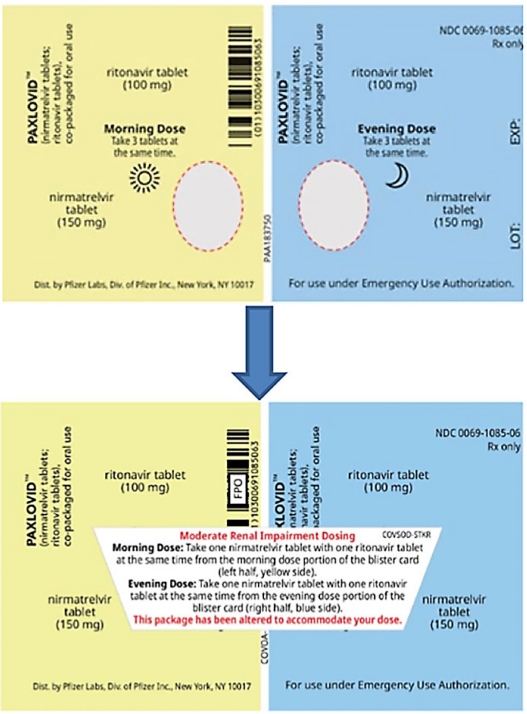
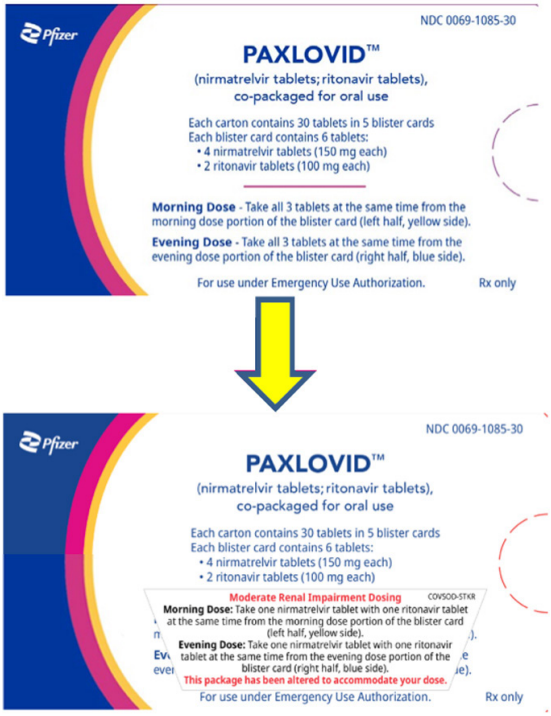
Considerations for therapy





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.

How should drug-drug interactions with Paxlovid be managed?

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.

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.

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Considerations for therapy

Pharmacists should refer to the Paxlovid's Fact sheet for healthcare providers for a complete list of serious drug interactions. In addition to the fact sheet for healthcare providers and screening checklist linked above, there are additional tools to assist providers in the assessment of drug-drug interactions:

- Liverpool COVID-19 Drug Interaction Checker
- Michigan Medicine Paxlovid Drug-Drug Interaction Management Tool

Is Paxlovid safe to take during pregnancy?

Clinical trials excluded pregnant or breastfeeding individuals; however, the mechanism of action for both nirmaltrelvir and ritonavir and the results of animal studies suggest that Paxlovid can be used safely in this population. According to the National Institutes of Health (NIH), Paxlovid should be offered to pregnant and lactating individuals based on the results of a risk-benefit assessment. Patients who are pregnant and/or breastfeeding should discuss their options with their health care provider.

What are additional counseling points for Paxlovid?

- Some patients have reported recurrent COVID-19 rebound after completing a 5-day course of Paxlovid and recovering from COVID-19, including patients who were up to date with COVID-19 vaccination. A brief return of symptoms may be part of the natural history of COVID-19 infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status.
- COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative.
- Patients who experience COVID-19 rebound should follow CDC recommendations for isolation, and re-isolate for at least 5 days.

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.

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Considerations for therapy

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.

What are additional counseling points for molnupiravir?

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.

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.

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Considerations for therapy

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.