

Guide to the Outpatient Management of Mild-Moderate COVID Disease: Focus on Oral Medications

New therapeutic options have arrived for the outpatient management of the mild-moderate COVID-19 disease in the form of oral medications: **Paxlovid** (nirmatrelvir and ritonavir) and **molnupiravir**. Below is information on these new treatments, prescribing tips, and how they compare to existing options such as monoclonal antibodies.

What is Paxlovid?

Paxlovid is a combination of nirmatrelvir and ritonavir. Nirmatrelvir is a 3CL-like protease inhibitor, an enzyme specific to coronaviruses, and is the main component of Paxlovid. Ritonavir is added to increase the half-life of the nirmatrelvir via inhibition of the CYP3A pathway.

In the EPIC-HR Phase 2/3 clinical trial, Paxlovid reduced the risk of hospitalization and death by 89% in high-risk persons when given within 3 days of symptom onset. If given within 5 days, the risk of hospitalization and death was reduced by 88%. It was authorized by the FDA for emergency use for the outpatient treatment of mild-moderate COVID-19 in high-risk persons.

Adverse events were similar in the Paxlovid and placebo groups (23 vs. 24%). Noted adverse effects with Paxlovid include impaired sense of taste, diarrhea, increased blood pressure, hepatotoxicity, and myalgias.

Paxlovid is approved for use under the EUA for the treatment of mild-moderate COVID disease with a symptom duration of five days or less in persons aged 12 years and older who weigh at least 40 kg and who have risk factors for progression to severe COVID disease. It is **not** approved for use in hospitalized patients or for pre- or post-exposure prophylaxis.

Paxlovid is not recommended for use in persons with severe renal impairment (eGFR <30 mL/min) or severe hepatic impairment (Child-Pugh Class C). It is contraindicated in persons who are being treated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions and that are potent CYP3A inducers which can significantly reduce plasma concentrations and effectiveness of Paxlovid. The list of medications is extensive and includes antiarrhythmics, antidepressants, HMG CoA reductase inhibitors (statins), and HIV antiretrovirals; providers should refer to the [Paxlovid Fact Sheet for Providers, Section 7](#).

Paxlovid is prescribed as 300mg of nirmatrelvir (2 150mg tablets) with 100mg of ritonavir (1 tablet) twice a day for a total of five days.

What is molnupiravir?

Molnupiravir is a novel antiviral agent that acts as a prodrug to a nucleoside analog. It interacts with the viral RNA polymerase to introduce mutations that ultimately have an antiviral effect (a mechanism referred to as “error catastrophe”).

In the MOVE-OUT Phase 2/3 clinical trial, molnupiravir reduced the risk of hospitalization and death by 30% when given to high-risk adult persons within 5 days of symptom onset.

No serious adverse events were noted in the study. Common adverse effects of molnupiravir include nausea, diarrhea, headache, rashes, insomnia, and liver test abnormalities.

Molnupiravir is approved for use under the EUA for the treatment of mild-moderate COVID disease with a symptom duration of five days or less in persons aged 18 years and older who have risk factors for progression to severe COVID disease. It is **not** approved for use in hospitalized patients or for pre- or post-exposure prophylaxis.

Molnupiravir is contraindicated in pregnant women as *in vitro* studies raised concerns about potential teratogenic effects. Women of childbearing age should be assessed for pregnancy. Women of childbearing age should use appropriate contraception while on molnupiravir and for at least four days after treatment. Breastfeeding is not recommended while on treatment and for at least four days afterwards. Males of reproductive potential should use contraception during treatment and for at least three months after the last dose.

Molnupiravir is prescribed as 800mg (4 200mg tablets) twice daily for a total of five days.

Are these oral agents active against the Omicron variant?

Both Paxlovid and molnupiravir are expected to be active against a range of SARS-CoV-2 variants, including Omicron.

What is a high-risk patient? Which patients should I prescribe these agents to?

Both oral agents as well as the COVID monoclonal antibody sotrovimab will be available in limited quantities during the winter. Patients should be prioritized based on their risk for progression to severe COVID disease and possible need for hospitalization. New York State Department of Health has provided a framework, with **persons belong to Tier 1A receiving the highest priority:**

Tier 1: Prioritization Groups for the Treatment of COVID-19		
For treatment, patients must have mild to moderate symptoms, test positive for SARS-CoV-2, and be within 10 days of symptom onset for mAbs or within 5 days for oral antivirals		
Risk Groups	Recommended Therapy/Approach	Notes on Prioritization
1A. Any age with moderate to severe immunocompromise regardless of vaccine status or Age 65 and older and not fully vaccinated with at least one risk factor for severe illness	Refer for monoclonal antibody therapy (mAb) or prescribe Paxlovid, ideally within 24 hours of positive test Consider molnupiravir if the options above are not available	If needed, prioritize patients based on <ul style="list-style-type: none"> • Age • Number of risk factors
1B. Under 65 years of age and not fully vaccinated with two or more risk factors for severe illness or over 65 and not fully vaccinated (no risk factors)	Consider mAbs or OAVs if supplies allow	If needed, prioritize patients based on <ul style="list-style-type: none"> • Age • Number of risk factors
1C. Under 65 years of age and not fully vaccinated with at least one risk factor for severe illness	Consider mAbs or OAVs if supplies allow	If needed, prioritize patients based on <ul style="list-style-type: none"> • Age
1D. Over age 65 and fully vaccinated with at least one risk factor for severe illness	Consider mAbs or OAVs if supplies allow	If needed, prioritize patients based on <ul style="list-style-type: none"> • Age • Number of risk factors • Receipt of booster • Time since last vaccination
1E. Under 65 years of age and fully vaccinated with at least one risk factor for severe illness or Age 65 and older and fully vaccinated with no other risk factors	Consider mAbs or OAVs if supplies allow	If needed, prioritize patients based on <ul style="list-style-type: none"> • Age • Number of risk factors • Receipt of booster • Time since last vaccination

Note that the NYSDOH framework is more restrictive than the FDA EUA for both agents. Providers are expected to adhere to this framework and prioritize persons in Tier 1A for outpatient treatments while shortages of these medications persist.

Can I use Paxlovid or molnupiravir in hospitalized patients?

Neither agent is approved under the FDA EUA for the treatment of hospitalized persons. With few exceptions, hospitals in New York state will not have direct access to the medications as they will not be allocated any supply.

Can I combine treatments (i.e., Paxlovid with sotrovimab)?

There is no clinical data to support the combination of COVID therapeutics in mild-moderate disease. In the setting of limited supplies of these medications, combining therapeutics is strongly discouraged.

How do I choose a COVID treatment for my patient with mild-moderate disease?

The preferred outpatient treatments for the mild-moderate COVID are sotrovimab and Paxlovid. Both are highly effective at decreasing the risk of hospitalization or death when given within five days of symptom onset (88% for Paxlovid vs. 85% for sotrovimab) and have good safety profiles in the clinical trials.

Choosing between sotrovimab and Paxlovid depends mostly on the local availability of the medications. In those patients who are at risk for significant drug interactions with Paxlovid, sotrovimab is preferred.

If outpatient treatment with a three-day course of remdesivir is available, this can be used as an alternative to sotrovimab and Paxlovid. This intervention has been demonstrated to reduce the risk of hospitalization and death by 87%.

If the above treatments are not available, molnupiravir can be considered. It can also be considered in persons with significant renal or hepatic impairment in lieu of Paxlovid when sotrovimab is not available. Molnupiravir is contraindicated in pregnant women. Patient of reproductive potential should be counselled on taking appropriate contraception measures as noted above.

All therapies for the treatment of mild-moderate COVID disease should be initiated as soon as possible and within five days of symptom onset.

Where does my patient get these oral COVID medications?

NYSDOH will distribute Paxlovid and molnupiravir to select pharmacies. Prescriptions should be sent to those specific pharmacies to minimize delays in treatment. The number of participating pharmacies is expected to grow as the medications become more available. Refer to the NYSDOH for listings of participating pharmacies.

Local Participating Pharmacies (as of December 28, 2021):

County	Store#	Store Name	City	ZIP
Nassau	997	CVS	GLEN COVE	11542
Nassau	2028	CVS	HEMPSTEAD	11550
Nassau	1084	CVS	FREEPORT	11520
Suffolk	3099	CVS	BAY SHORE	11706
Suffolk	6026	CVS	RIVERHEAD	11901
Suffolk	1271	CVS	ROCKY POINT	11778
Suffolk	2961	CVS	HUNTINGTON STATION	11746