Northwestern Medicine ADSP/ID COVID Guidance for Outpatient Therapy

Careful clinical consideration should be applied when deciding to use the agents listed in this guidance document. Evidence is continuing to evolve and this guidance will be updated accordingly.

	Nirmatrelvir/ritonavir (Paxlovid™)	Molnupiravir (Lagevrio™)	Remdesivir (Veklury®)
Class	Antiviral, SARS-CoV-2 main protease (Mpro) inhibitor/HIV-1 protease inhibitor	Antiviral, Nucleoside inhibitor	Antiviral, RNA polymerase inhibitor
Age Limitations	12 years and older weighing at least 40 kg	18 years and older	28 days and older weighing at least 3 kg
Dose	300 mg PO nirmatrelvir (2-150 mg tabs) + 100 mg PO ritonavir TWICE daily x 5 days	800 mg PO TWICE daily x 5 days (4-200 mg caps)	200 mg IV infusion once on Day 1 then 100 mg IV daily on Days 2-3
Duration	5 days	5 days	3 days
Admin Route	Oral (Do not crush)	Oral (Do not crush)	Intravenous
Dose Adjustments	Renal: • eGFR ≥30-59: Nirmatrelvir 150 mg + 100 mg ritonavir TWICE daily • eGFR <30: Not recommended Hepatic: • Child-Pugh C: Not recommended	None	Renal: • eGFR <30: Risk vs. benefit, limited duration of therapy may reduce risk of renal injury Hepatic: • ALT >10x ULN or ALT ↑ w/liver inflammation: Not recommended
Drug-Drug Interactions	****Significant CYP3A interactions** – see Appendix B below	None	Avoid co-administration with HCQ or CQ due to antagonistic effects
Warnings/ Contraindications	• Co-administration with CYP3A substrates that pose serious risk at elevated concentrations • Co-administration with CYP3A inducers (decreased Paxlovid™ concentrations) • Hepatotoxicity • HIV-1 resistance among untreated or non-virally suppressed patients • Hypersensitivity • Use non-hormonal contraception	• Embryo-Fetal toxicity ○ Avoid use in pregnancy ○ Childbearing females should use reliable contraception during tx & 4 days after last dose ○ Males should use reliable contraception during tx & 3 months after last dose • Bone & Cartilage toxicity ○ Avoid in pts age <18 yr	• Caution in patients with eGFR <30 mL/min as IV formulation contains cyclodextrin, although use should be considered with risk-benefit assessment • Hypersensitivity
Adverse Events	Dysgeusia, diarrhea, hypertension, myalgias	Diarrhea, nausea, dizziness	Hepatotoxicity, abnormal INR/PT/PTT, nephrotoxicity, bradycardia, nausea, headache, anaphylaxis
Requires EUA documentation	Yes	Yes	No, FDA approved indication
	Patient EUA Information Sheet available on asp.nm.org. Any side effects should be reported to FDA MedWatch http://www.fda.gov/medwatch		

Select Evidence	**Nirmatrelvir/ritonavir (Paxlovid™)**	**Molnupiravir (Lagevrio™)**	**Remdesivir (Veklury®)**
Primary Trial	EPIC-HR (NCT04960202) *Completed*	MOVe-OUT (NCT04575597) *Trial Completed Early*	PINETREE (NCT04501952) *Completed*
Population studied	High-risk outpatients with mild to moderate COVID-19, enrolled within 5 days of symptom onset Included unvaccinated patients only	High-risk outpatients with mild to moderate COVID-19, enrolled within 5 days of symptom onset Included unvaccinated patients only	High-risk outpatients with mild to moderate COVID-19, enrolled within 7 days of symptom onset Included unvaccinated patients only
Relative Risk Reduction (RRR)	88% (95% CI 75-94%)	31% (HR 0.69, 95% CI 0.48-1.01)	87% (95% CI 41-99%)
NNT, Hosp or Death	18	34	22
Adverse Event Rate	2% Paxlovid v 4% placebo (Treatment discontinuation due to adverse event)	Any AE 30.4% molnupiravir v 33% placebo; Serious AE 7% v 10% placebo	42.3% RDV v 46.3% placebo
Inpatient use per EUA ***May differ from NM policy***	Continuation of outpt therapy allowed. Not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.	Continuation of outpt therapy allowed. Not authorized for treatment in patients requiring hospitalization due to COVID-19.	Also approved for COVID-19 treatment of hospitalized patients. Recommended duration is 5 days for inpatients or 10 days if the patient requires mechanical ventilation or ECMO.

Appendix A. Risk Stratification & Treatment Recommendations

- Patients should be non-hospitalized and COVID-19 positive with mild to moderate disease (not hypoxic requiring oxygen nor increase in baseline oxygen requirement) with onset of symptoms within 5[#] days who are at high risk of disease progression

Priority Group	Criteria	Recommended Therapy	Alternative Agent
Tier 1A	Moderately and severely immunocompromised patients per CDC definitions: ○ Active tx for solid tumor or hematologic malignancy ○ Receipt of solid-organ transplant and active use of immunosuppressive therapy ○ Receipt of CAR T-cell therapy of HCT – within prev 2 yrs or requiring active use of immunosuppressive therapy ○ Mod to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome) ○ Advanced or untreated HIV infection – people living with HIV and having CD4 cell counts <200/mm^3, Hx of AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV ○ Active use of high-dose corticosteroids (i.e., >20 mg prednisone/day or equivalent for duration >2 weeks) ○ Active use of severely immunosuppressive cancer chemotherapeutics, alkylating agents, antimetabolites, tumor necrosis factor blockers, and other immunosuppressive biologic agents	For patients not on concurrent medications that interact with Paxlovid™ and have high-risk for toxicity (See Appendix B for Drug Interaction Guidance) **Paxlovid™ PO twice daily x 5 days** ○ Prescriber must send prescription to participating pharmacy	For patients with contraindications to or on concurrent medications that interact with Paxlovid™: **Molnupiravir PO twice daily x 5 days** ○ Avoid use in pregnancy or those trying to become pregnant
Tier 1B	Unvaccinated pregnant patients with 1 or more risk factors* Unvaccinated patients with 3 or more risk factors*		
Tier 3	Unvaccinated patients with 1 to 2 risk factors*		
Tier 4	Vaccinated patients with 1 to 2 risk factors*		

[#]Patients should receive Paxlovid™ or molnupiravir within 5 days of symptom onset

*Clinical Risk Factors for Progression to Severe COVID-19				
Older age (≥ 50 years)	Pregnancy	Chronic lung disease (COPD, ILD, CF, pulmonary hypertension, moderate to severe asthma)	Sickle cell disease	Immunosuppressive disease or medications
Obesity (BMI ≥ 30 kg/m^2)	Diabetes	Cerebrovascular disease or neurodevelopmental disorders including cerebral palsy, genetic or metabolic syndromes, congenital abnormalities	Chronic kidney disease	Use of tracheostomy, gastrostomy, positive-pressure ventilation
Cardiovascular disease or hypertension			Chronic liver disease	Cancer

Appendix B. Notable Drug-Drug Interactions for Nirmatrelvir/Ritonavir (Paxlovid™)

Patients who are taking any of the following medications should NOT be prescribed Paxlovid™ (agents listed alphabetically): Amiodarone, Apalutamide, Bosentan, Carbamazepine, Cisapride, Clopidogrel, Clozapine, Colchicine, Cyclosporine, Disopyramide, Dofetilide, Dronedarone, Eplerenone, Ergot derivatives, Everolimus, Flecainide, Flibanserin, Glecaprevir/pibrentasvir, Ivabradine, Lumateperone, Lurasidone, Mexiletine, Phenobarbital, Phenytoin, Pimozide, Propafenone, Quinidine, Ranolazine, Rifapentine, Rivaroxaban, Sildenafil for pulmonary hypertension, Sirolimus, St. John's wort, Tacrolimus, Tadalafil for pulmonary hypertension, Ticagrelor, Vorapaxar

Patients who are taking any of the following medications *and are unable to be switched to a comparable alternative OR unable to hold these agents while taking Paxlovid™ and for 5 days after completion of therapy* should NOT be prescribed Paxlovid™ (agents listed alphabetically): Alfuzosin, Alprazolam, Atorvastatin, Avanafil, Clonazepam, Codeine, Diazepam, Fentanyl, Hydrocodone, Lomitapide, Lovastatin, Meperidine, Midazolam, Piroxacam, Propxyphene, Rosuvastatin, Salmeterol, Sildenafil for erectile dysfunction, Silodosin, Simvastatin, Suvorexant, Tadalafil for erectile dysfunction, Tamsulosin, Tramadol, Triazolam, Vardenafil

Drug-Drug Interaction Checker: University of Liverpool COVID-19 Therapy Drug-Drug Interaction Checker

Northwestern Medicine Antimicrobial Stewardship & Infectious Diseases Clinical Pharmacists available if questions:
Page Pharmacist COVID Support (pg 17703) OR 312-695-5955 OR Email: nmhaspconsult@nm.org

AVOID Co-administration with potent CYP3A Inducers – concentrations of Paxlovid™ reduced & may lead to inefficacy of Paxlovid™

Co-administered agent	Interaction	Recommendation
Carbamazepine Phenobarbital Phenytoin	↓ Concentrations of nirmatrelvir/ritonavir (Paxlovid™) causing potential loss of virologic response and possible resistance. ○ ↑ Concentrations of carbamazepine ○ ↓ Concentrations of phenobarbital & phenytoin	Avoid use of Paxlovid™. Recommend alternative therapy.
Rifampin	↓ Concentrations of nirmatrelvir/ritonavir (Paxlovid™) causing potential loss of virologic response and possible resistance.	Avoid use of Paxlovid™. Consider alternative anti-mycobacterial therapy such as rifabutin.
St. John's Wort	↓ Concentrations of nirmatrelvir/ritonavir (Paxlovid™) causing potential loss of virologic response and possible resistance.	Avoid use of Paxlovid™. Recommend holding agent or using alternative therapy.
Apalutamide	↓ Concentrations of nirmatrelvir/ritonavir (Paxlovid™) causing potential loss of virologic response and possible resistance.	Avoid use of Paxlovid™. Recommend alternative therapy.

Sources: NIH Treatment Guideline Statement on Paxlovid Drug-Drug Interactions, IDSA Guideline on the Treatment and Management of COVID-19 & Paxlovid EUA Fact Sheet for Healthcare Providers