Northwestern Medicine ASP/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, as such this guidance will be updated accordingly.

Agent	Sotrovimab	Nirmatrelvir/ritonavir (Paxlovid)	Molnupiravir (Lagevrio)	Remdesivir (Veklury)
Class	Anti-spike monoclonal antibody (mAb)	Antiviral, SARS-CoV-2 main protease (Mpro) inhibitor/HIV-1 protease inhibitor	Antiviral, Nucleoside inhibitor	Antiviral, RNA polymerase inhibitor
Dose	500mg IV infusion over 30min once	300mg PO nirmatrelvir (2-150mg tabs) + 100mg PO ritonavir TWICE Daily for 5 days	800mg PO TWICE Daily for 5 days (4-200mg caps)	200mg IV infusion once on Day 1 then 100mg IV once daily on Days 2-3
Duration	One-time	5 days	5 days	3 days
Admin Route	Intravenous	Oral (Do not crush)	Oral (Do not crush)	Intravenous
Dose Adjustments	None	Renal: • eGFR ≥30-59: Nirmatrelvir 150mg + 100mg ritonavir TWICE daily • eGFR <30: Not recommended Hepatic: • Child-Pugh C: Not recommended	None	Renal: • eGFR <30: Risk v 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	None	**Significant CYP3A interactions – see Appendix B below	None	Avoid co-administration with HCQ or CQ due to antagonistic effects
Warnings/ Contraindications	• Infusion related reactions	• 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 • Non-hormonal contraception should be used	• Embryo-Fetal toxicity ○ Avoid use in pregnancy ○ Childbearing females should use reliable contraception during tx & 4d after last dose ○ Males should use reliable contraception during tx & 3 months after last dose • Bone & Cartilage toxicity ○ Avoid in pts age <18 yo	• 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	Injection site pain	Dysgeusia, diarrhea, hypertension, myalgia	Diarrhea, nausea, dizziness	Hepatotoxicity, abnormal INR, PT & PTT, nephrotoxicity, bradycardia, nausea, headache, anaphylaxis
Requires EUA documentation	Yes	Yes	Yes	Off-label, FDA Approved for inpt use
	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	Sotrovimab	Nirmatrelvir/ritonavir (Paxlovid)	Molnupiravir (Lagevrio)	Remdesivir (Veklury)
Primary Trial	COMET-ICE (NCT04545060) *Interim Analysis Only*	EPIC-HR (NCT04960202) *Recruiting, Press Release Only*	MOVe-OUT (NCT04575597) *Trial Completed Early*	PINETREE (NCT04501952) *Completed*
Population studied	High-risk* Outpatients with mild to moderate COVID-19, given mAb within 5 days of symptom onset	High-risk Outpatients with mild to moderate COVID-19, enrolled within 5 days of symptom onset Included non-vaccinated patients only	High-risk Outpatients with mild to moderate COVID-19, enrolled within 5 days of symptom onset Included non-vaccinated patients only	High-risk Outpatients with mild to moderate COVID-19, enrolled within 7 days of symptom onset Included non-vaccinated patients only
Relative Risk Reduction (RRR)	79% (95% CI 50-91%)	88% (95% CI 75-94%)	31% (HR 0.69, 95% CI 0.48-1.01)	87% (95% CI 41-99%)
NNT, Hosp or Death	22	18	34	22
Adverse Event Rate	17% mAb v 19% placebo	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	If admitted for reasons other than COVID-19 & w/out severe/critical illness	Continuation of outpt therapy allowed. If admitted for reasons other than COVID-19 & w/out severe/critical illness	Continuation of outpt therapy allowed. If admitted for reasons other than COVID-19 & w/out severe/critical illness	If admitted for reasons other than COVID-19 & w/out severe/critical illness

*High-risk factors included but not limited to Age >60 years, active cancer, CKD, COPD, BMI ≥30, CHF, CAD, cardiomyopathy, diabetes

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 req) with onset of symptoms within 5[#] to 10^ 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) **1. Paxlovid PO Twice daily x5 days** ○ Prescriber must send prescription to participating pharmacy **OR** **2. Sotrovimab IV infusion once, if risk of DDI with Paxlovid** ○ Prescriber must place referral order For patients on concurrent medications that interact with Paxlovid **1. Sotrovimab IV infusion once** ○ Prescriber must place referral order	**Molnupiravir PO Twice daily x5 days** ○ Avoid use in pregnancy or those trying to become pregnant
Tier 1B	Unvaccinated patients with 3 or more risk factors*		
Tier 2	Vaccinated patients with 3 or more risk factors*	For patients not on concurrent medications that interact with Paxlovid (See Appendix B for Drug Interaction Guidance) **1. Paxlovid PO Twice daily x5 days**	**Molnupiravir PO Twice daily x5 days**
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

^Patients should be referred for and receive sotrovimab IV infusion within 10 days of symptom onset, with evidence-based benefit seen with use within 5 days of symptom onset

*Clinical Risk Factors for Progression to Severe COVID-19				
Older age (≥65 years)	Pregnancy	Chronic lung disease (COPD, ILD, CF, pulmonary hypertension, moderate to severe asthma)	Sickle cell disease	Immunosuppressive disease or treatment
Obesity (BMI ≥30 kg/m^2	Diabetes	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	

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 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