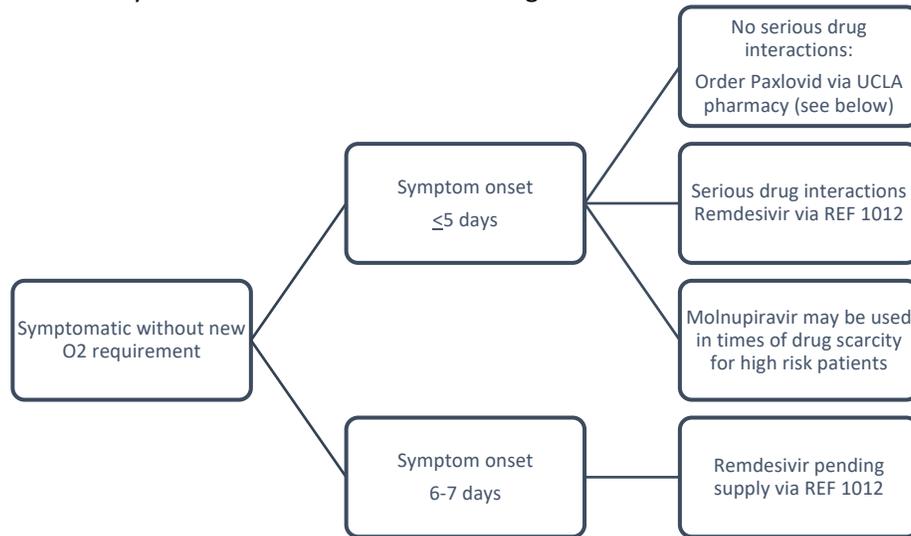


1. Background:

The National Institutes of Health (NIH) Covid-19 Treatment Panel¹ has recommended the use of several treatments for **outpatients with symptoms of mild-moderate COVID-19 who are at high risk for progression to severe infection.**

2. Eligibility/Patient Selection:

Each patient should only be offered one treatment during the course of infection.



As of November 2022, the available monoclonal antibodies are not effective against the predominant variants.

Remdesivir is primarily reserved for moderate-severely immunocompromised patients or patients requiring oxygen at baseline who are unable to take Paxlovid due to drug interactions.

2.1 Treatment requirements*:

Patients must meet **all** the following criteria to be eligible for any outpatient treatment at UCLA:

- Not requiring any supplemental O2 or increase from baseline O2 requirements
- Symptom onset ≤ 7 days prior (≤ 5 days for Paxlovid and molnupiravir)
- At least one high-risk criterion (see below)

*A positive SARS-CoV2 test is preferred and rapid antigen or PCR are acceptable. Paxlovid may be prescribed for high risk travelers with strict counseling of conditions and drug interactions.

2.2 High risk criteria:

- Age ≥ 65 regardless of medical co-morbidities
- Diabetes
- Immunosuppressive disease or immunosuppressive therapy (see below)
- CKD (CrCl < 60 ml/min per Cockcroft-Gault for > 3 months)
- Obesity (BMI ≥ 25 or if 12-17 years BMI $\geq 95^{\text{th}}$ percentile (based on CDC growth chart))
- Neurologic diseases: cerebrovascular diseases, Down Syndrome or other neurodevelopmental disorders, or dementia
- Pregnancy if other risk factors and under maternal fetal medicine consultation (consider checking antibody status)
- Hemoglobin disorders (sickle cell, thalassemia)

- Hypertension OR Cardiovascular disease (congenital heart disease, heart failure, CAD, cardiomyopathy, or pulmonary HTN)
- Chronic lung disease (COPD/emphysema, moderate-severe asthma, CF, pulmonary fibrosis)
- Medical-related technological dependence (tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19)
- Other CDC defined high risk criteria including history of smoking, history of cancer, liver disease, well controlled HIV, mental health disorders and substance use disorders
- Socioeconomically disadvantaged patients considered given increased risk of mortality.

2.3 Prioritization in times of scarcity:

The following tiered strategy modified from [the NIH](#) approach will be implemented during times when referrals exceed supply. Treatment of COVID-19 in unvaccinated/ incompletely vaccinated individuals with clinical risk factors for severe illness and/or vaccinated who are unable to mount an adequate immune response (i.e., immunocompromising conditions).

Tier 1	Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors) OR Individuals with severe immunocompromising conditions not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (highest risk)
Tier 2a	Tier 2A - Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged ≥ 65 years or anyone aged < 65 years with clinical risk factors based on criteria above) or Moderate-severe immunocompromise (per CDC criteria) not otherwise included in Tier 1, regardless of vaccine status and age
Tier 3*	Vaccinated individuals at high risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with high risk criteria other than immunosuppression)

*Pending supply Tiers 3

Severe immunocompromising conditions (Tier 1):

- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant)
- Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm³

Moderate immunocompromising conditions (Tier 2B):

- Active cancer treatment for non-hem malignancies (e.g. myelosuppressive chemotherapy)
- Solid organ transplant on immunosuppression (>1 year)
- HSCT <2 years (without GVHD/not taking immunosuppressive meds for another indication)
- Moderate primary immunodeficiency on treatment

- Untreated/advanced HIV, CD4 count <200 but >50 cells/mm³
- Active treatment with high-dose corticosteroids (>20mg daily for at least 2 weeks) or other drugs that may suppress your immune response (active, within the last month)

When demand exceeds supply on any given day, the order time stamp and a point system, specifically prioritizing risk of disease severity and risk of exposure (including socioeconomic vulnerability), will be included in the allocation process. A lottery system may also be utilized if multiple individuals have the same risk for disease severity. Referrals will be reviewed at 10:30am on each calendar day.

3. Selection of Therapies/Ordering:

Agents will be considered depending on availability, activity against circulating strain, and contraindications.

3.1 Available Options

- Paxlovid (PO), a protease inhibitor: many drug interactions
- Remdesivir (IV), a nucleotide prodrug analogue targeting RNA polymerase
- Molnupiravir (PO): nucleoside prodrug that targets RNA polymerase

Table 1: Available Options and Considerations

	Paxlovid (nirmatrelvir/ritonavir)	Remdesivir	Molnupiravir
Standard Dose	Nirmatrelvir 300mg (two 150 mg tablets) with 100 mg ritonavir (one 100mg tablet) PO, with all three tablets taken together twice daily for 5 days with or without food	200mg IV day 1 100mg IV days 2-3	800mg po BID x 5 days
Window	5 days from sx onset	7 days from sx onset	5 days from symptom onset
Efficacy	89% risk reduction in hospitalization	87% risk reduction in hospitalization	30% reduction in hospitalization
Drug Interactions	-Substrate and inhibitor of CYP3A4 - Review Appendix A , the prescribing information, and https://www.covid19-druginteractions.org/checker	No significant interactions; hydroxychloroquine lowers remdesivir activity	No significant interactions identified, based on limited data
Pregnancy/Lactation	Limited data, <u>must be approved by MFM</u>	Limited data, generally considered safe	Contraindicated
Renal adjustment	-For eGFR ≥30 ml/min and ≤60 ml/min: decrease dose to 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) twice daily x 5 days with or without food -Not recommended for eGFR < 30 ml/min	No dosage adjustment recommended in patients with any degree of renal impairment, including patients on dialysis	No adjustments
Hepatic adjustment	Not recommended in severe impairment	No dosage adjustment recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Discontinue if AST/ALT increase >10 x ULN on therapy	No adjustments

3.2 Dispensing Requirements

Drug interactions must be reviewed prior to prescribing Paxlovid (see Table below or use <https://www.covid19-druginteractions.org>).

3.3 How to order/refer to outpatient therapies (IV only):

- Provider places order for REF1012 (**Referral for COVID-19 Outpatient Therapies**)
- Patient is assessed by Outpatient COVID-19 Treatment Team and, if eligible, scheduled for outpatient infusion at the immediate care center in 200 Medical Plaza

3.4 Oral Antivirals (Paxlovid or Molnupiravir) Ordering:

E-prescriptions for Paxlovid (nirmatrelvir-ritonavir) or molnupiravir can be sent directly to the below pharmacies for curbside pickup if supply is available.

- **Medical Plaza Level 1 Pharmacy** - Hours: Mon-Fri 8a-6p, Sat 8a-4p; 310-794-1170

- **UCLA Santa Monica 16th Street Pharmacy** - Hours Mon-Fri 8a-6p, Sat 8a-5p; 424-259-8520

3.4.1 Screenshot of Liverpool Covid Drug interactions website

Paxlovid DDI Resources – Liverpool COVID-19 Drug Interactions Checker

The screenshot displays the Liverpool COVID-19 Drug Interactions Checker interface. At the top, there is a green header with the site name and navigation links. Below the header, a green banner provides a summary of interactions. The main content area is divided into three columns: COVID Drugs, Co-medications, and Drug Interactions. In the COVID Drugs column, 'paxlovid' is entered, and search results for 'Nirmatrelvir/ritonavir (5 days)' are shown. In the Co-medications column, 'apixab' is entered, and search results for 'Apixaban' are shown. The Drug Interactions column shows a red box with the text 'Do Not Coadminister' and a warning: 'Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]'. Below this, the drug 'Apixaban' is listed, and a red circle highlights the 'More Info' link. A red arrow points from the 'More Info' link to the warning text. On the left side of the screenshot, there is a list of instructions: '-Updated frequently', '-Easiest to search', '-Be sure to click "More Info" for details on management recommendations'.

3.5 Emergency Department Guidance:

Patients should NOT be referred to the ED specifically for treatment. Socioeconomically vulnerable patients unable to access care otherwise will be prioritized and can be discussed with the on-call ID team.

In addition, patients who meet the criteria for Paxlovid (high risk, symptoms ≤ 5 days and no contraindicated drug interactions) can have the medication ordered at the 200 Med Plaza Level 1 pharmacy or the SM 16th street pharmacy (see Section 3.4 and 3.4.1 above).

Additional resources for therapeutics outside UCLA:

<https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/>

Patient facing website on UCLA treatment approach

<https://www.uclahealth.org/conditions-we-treat/coronavirus/covid-19-outpatient-treatments>

References: <https://www.covid19treatmentguidelines.nih.gov>

Appendix A: Paxlovid Drug Interactions – Modified from NIH Table¹

Tier 1) Prescribe an alternative COVID-19 therapy for patients who are receiving any of the medications listed.

- Aldosterone antagonists/K+-sparing diuretics: Eplerenone
- Antiarrhythmics: Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ivabridine, mexiletine, propafenone, quinidine
- Antianginal: Ranolazine (if used as an antiarrhythmic)
- Anticoagulants: Apixaban/rivaroxaban (if used for VTE)
- Antiplatelet: Clopidogrel (if within 6 weeks of stenting), Ticagrelor, vorapaxar
- Antipsychotics: Lurasidone, pimozide, clozapine, lumateperone
- Benzodiazepines: Midazolam (oral)
- Cystic fibrosis: Lumacaftor-ivacaftor
- Ergot derivatives: Dihydroergotamine, ertogamine, methylegonovine
- Gout: Colchicine (if taking daily for gout prevention and severe hepatic/renal impairment)
- Hepatitis C antivirals: Glecaprevir/pibrentasvir
- Immunosuppressants: Cyclosporine, everolimus, sirolimus, tacrolimus, voclosporin
- Opioids: Fentanyl, meperidine
- PDE5 Inhibitors: Sildenafil, tadalafil, vardenafil (if used for pulmonary hypertension)
- Pulmonary HTN: Bosentan
- Strong CYP3A4 inducers: Apalutamide, carbamazepine, phenobarbital/primidone, phenytoin, rifampin, rifapentine, St. John's Wort
- Misc: Flibanserin, lomitapide, tolvaptan

Tier 2) If the patient is receiving any of these medications, hold or dose adjust the concomitant medication if clinically appropriate (see individual agents for specific instructions). If withholding is not clinically appropriate, use an alternative COVID-19 therapy.

Generally, ritonavir inhibitory effects are no longer present three days after final dose, this effect can be prolonged in elderly patients/renally impaired. Agents with wide therapeutic index/low risk of severe outcome **can be held for 8 days** from first Paxlovid dose, narrow therapeutic **index/high toxicity risk agents may need to be held for 10 days**.

- Anticoagulants: Apixaban/rivaroxaban for Atrial fibrillation
 - Rivaroxaban: can hold x 10 days
 - Apixaban: reduce to 2.5 mg BID and resume usual dose 3 days after completing Paxlovid
 - If patient is already on apixaban 2.5 mg BID, can continue on case-by-case basis after discussion with MAB team
- Alpha-1 Antagonists: Alfuzosin, sildosin, tamsulosin – Can hold x 8 days
- Antiplatelet: Clopidogrel – Discuss risk of diminished platelet inhibition with provider
- Benzodiazepines: Alprazolam*, clonazepam, diazepam, midazolam (oral), triazolam – Can hold x 8 days; *alprazolam dose can be decreased by 50% with monitoring
- Contraceptives (oral combination): Consider backup non-hormonal contraceptive
- Chemotherapy (oral): Consult individual agent drug interactions, discuss any adjustments with hem-onc provider
- Gout: Colchicine – if taking PRN and no severe hepatic/renal impairment – Can hold x 10 days
- Long-acting beta agonists (inhaled): Salmeterol (Brand names: Serevent, Wixela; Component of Advair Diskus) – Can hold x 8 days; Can consider temporary substitution with non-salmeterol LABA (e.g. formoterol-based [Dulera, Symbicort])
- Opioids: Codeine, ^hydrocodone, ^oxycodone, meperidine, tramadol – Can hold x 10 days; ^oxycodone dose can be decreased by 75% with monitoring, hydrocodone dose can be decreased by 50% with monitoring
- PDE5 Inhibitors: Avanafil, sildenafil, tadalafil, vardenafil – Can hold x 8 days if used for erectile dysfunction
- Statins: Atorvastatin, lovastatin, rosuvastatin, simvastatin – Can hold x 8 days