COVID-19 Pharmacotherapy Guidance

Management of Non-Hospitalized Adults

PATIENT DISPOSITION	RECOMMENDATIONS
Symptomatic, not requiring hospitalization or supplemental oxygen	Follow the outpatient treatment algorithm (**Page 2**) to determine eligibility for **bebtelovimab, nirmatrelvir/ritonavir (Paxlovid)**, **remdesivir (Veklury)** or **Molnupiravir.** *Note: No specific therapy is authorized for patients who test positive but are asymptomatic.*
Discharged from hospital, not requiring supplemental oxygen	No specific antiviral or immunomodulatory therapy recommended.
Discharged from hospital, requiring supplemental oxygen *For those stable enough for discharge but still requiring oxygen*	Consider: continuing **dexamethasone** for the duration of supplemental oxygen requirement, up to 10 days total duration, with close monitoring for adverse events.
Discharged from ED or urgent care, despite new oxygen requirement *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*	**Dexamethasone** daily for the duration of supplemental oxygen requirement or up to 10 days maximum, with close monitoring for adverse events.

Management of Hospitalized Adults

DISEASE SEVERITY	RECOMMENDATIONS
Symptomatic, not requiring supplemental oxygen	• No specific antiviral or immunomodulatory therapy is routinely recommended. • Consider **mAb** (if meets EUA criteria and product available). Convalescent plasma is no longer available for use. • Consider **remdesivir** x 3 days for those hospitalized patients with inadvertent COVID-19 diagnosis, mild-moderate symptoms, not needing oxygen supplementation for COVID-19, underlying conditions place at high-risk for progression, and in whom symptom onset is within 7 days. • *Note: No specific therapy is authorized for patients who test positive but are asymptomatic.*
Requiring low-flow supplemental oxygen	• Use: **Remdesivir** (if ≤ 7 days of symptom onset) *plus* **Dexamethasone**
Requiring oxygen via high-flow device or non-invasive ventilation	• Use: **Dexamethasone** • Consider: **Remdesivir if** early in the disease course (≤ 7 days of symptom onset) or immunocompromised host. • Consider: **Baricitinib**, in combo with dexamethasone, for recently hospitalized patients and rapidly increasing oxygen needs plus systemic inflammation. Tocilizumab may be considered if baricitinib is contraindicated. Consider assessing reponse to steroids before deciding whether baricitinib is needed.
Hospitalized, requiring mechanical ventilation or extra-corporeal membrane oxygenation	• For most patients, use **Dexamethasone** • Consider: **Baricitinib**, in combo with **dexamethasone**, for recently hospitalized patients and rapidly increasing oxygen needs plus systemic inflammation. • **Tocilizumab** may be considered if baricitinib is contraindicated and the patient is within 24hrs of ICU admission and mechanical ventilation.

Prevention of COVID-19 in Adults (Hospitalized or Non-Hospitalized)

PATIENT DISPOSITION	RECOMMENDATIONS
Pre-exposure prophylaxis (PrEP)	• **Tixagevimab-Cilgavimab** is authorized for PrEP in patients who are not infected or had recent SARS-CoV-2 exposure, AND have moderate to severe immune compromise and may not mount adequate immune response to COVID vaccination, OR for whom vaccination is not possible due to adverse reaction. *Note: Tix/Cil may have decreased effectiveness against Omicron variant and is not a substitute for vaccination*. *Availability TBD*
Post-exposure prophylaxis (PEP)	• **Casirivimab-Imdevimab** *or* **Bamlanivimab-Etesevimab** previously available for PEP in high-risk patients who are incompletely vaccinated or not expected to mount an adequate vaccine response. *These are currently not available/indicated due to Omicron spread and diminished mAb activity.* Bebtelovimab are not authorized for PEP.

COVID-19 Therapies: Outpatient Treatment Algorithm

Does the patient meet criteria for outpatient COVID-19 Treatment?

- Onset of symptoms and positive SARS-CoV-2 test within the past 7-days, **AND**
- Has mild-moderate COVID-19 symptoms (e.g., cough, fever, headache, malaise, fatigue), **AND**
- Does NOT require new or increasing oxygen supplementation for hypoxia due to COVID-19, **AND**
- Is NOT hospitalized due to COVID-19, **AND**
- 12 years of age and older weighing ≥ 40kg, **AND**
- Have ≥ 1 risk factor for progression to severe COVID-19[a]:

Is the patient pregnant or have a moderate to severe immunocompromising condition (see page 4 for complete list)?

No

Symptom onset?

≤ 5 days

Preferred: Paxlovid
- Assess for drug interactions, HIV status, and severe renal or hepatic dysfunction exclusions.

Alternatives, if unable to get Paxlovid:
1. Bebtelovimab
2. Remdesivir
3. Molnupiravir
   - If sotrovimab and remdesivir unavailable
   - **≥ 18 years old only**
   - Contraception counseling

6-7 days

Preferred: Bebtelovimab
- For ordering, follow instructions on the Source: COVID-19 resources mAb page.

Alternatives:
1. Remdesivir if within 7 days of symptom onset

Yes

Preferred: Bebtelovimab
- For ordering, follow instructions on the Source: COVID-19 resources mAb page.

Alternatives, if bebtelovimab unavailable:
- **Pregnant**:
  1. Remdesivir if within 7 days of symptom onset
  2. Paxlovid may be considered if within 5 days of symptom onset based on risk/benefit assessment

  **Molnupiravir is not recommended in pregnant or lactating individuals.*

- **Immunocompromised:**
  1. Remdesivir may be considered if within 7 days of symptom onset
  2. Paxlovid may be considered if within 5 days of symptom onset (assess for clinical exclusions – particularly interactions)
  3. Molnupiravir may be considered if within 5 days of symptom onset

[a]Risk factors for progression to severe disease

◊ Older age (age ≥ 65 years)
◊ Obesity or overweight (BMI ≥ 25 kg/m^2, or BMI ≥85th percentile if age 12-17 years)
◊ Pregnancy
◊ Chronic kidney disease
◊ Diabetes mellitus
◊ Immunosuppressive disease or treatment, including HIV infection
◊ Cardiovascular disease (including congenital heart disease and cerebrovascular disease)
◊ Hypertension
◊ Chronic lung disease (e.g., COPD, asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension, or current/former smoker)
◊ Sickle cell disease
◊ Neurodevelopmental disorders (e.g., cerebral palsy, genetic, metabolic syndromes or severe congenital abnormalities)
◊ Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation)
◊ Other medical conditions or factors placing an individual patient at high risk for progression to severe disease (e.g., race or ethnicity, people with disabilities, substance use disorder, others

COVID-19 Therapies: Indications, Drug Information, Ordering Information

Anti-SARS-CoV-2 Monoclonal Antibodies

COVID-19 monoclonal antibodies (mAbs) are laboratory-derived neutralizing antibodies against the SARS-CoV-2 spike protein. mAbs are available under EUA for outpatient treatment, post-exposure prophylaxis, or pre-exposure prophylaxis with potential inpatient use permitted in select cases. mAbs can prevent symptomatic COVID-19, shorten symptom duration, prevent hospitalization, and reduce mortality.

mAbs for Outpatient Treatment at UCHealth:

- **Bebtelovimab (Lilly)**: EUA granted for treatment indication only if within **7-days** of symptom onset. Active against currently circulating variants, including BA.1.1 and BA.2 sub-variants. Dosing is 175mg IV push over at least 30 seconds, followed by 0.9% sodium chloride flush. Patients should be observed for 1 hour.
- Sotrovimab, casirivimab/imdevimab, and bamlanivimab/etesevimab distribution and EUA status has been paused and are NOT recommended for treatment due to loss of *in vitro* activity in the presence of currently circulating variants.

Treatment Criteria	Treatment Exclusions
1. Confirmed COVID-19 (by PCR or antigen test) 2. Mild-moderate (symptomatic) disease, not requiring supplemental O2 3. Symptom duration ≤ 7 days 4. High risk for progression to severe disease (see EUA high-risk criteria below) 5. Age ≥12 years and weight ≥40kg	• Hospitalization due to COVID-19 • New oxygen requirement or increase in oxygen flow rate from baseline (SpO2 < 90%)

There is no longer a waiting period recommended after mAb treatment to receive COVID-19 vaccination.

mAbs for Pre-exposure prophylaxis at UCHealth:

- **Tixagevimab-Cilgavimab (Evusheld; AstraZeneca)**: EUA granted for pre-exposure prophylaxis. Retains activity against many circulating variants, including alpha, beta, gamma, and delta. The potency against Omicron is reduced ~100-fold; however, AstraZeneca suggests it may still have efficacy in prevention given the concentrations remain higher than Omicron's IC50 throughout the dosing interval. Currently available in limited supply at transplant centers only. Dosing is 300mg tixagevimab and 300mg cilgavimab both given as separate, consecutive 3mL IM injections. One hour observation after administration is recommended.

PrEP Criteria	Moderate-Severe IC conditions
Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 AND: a. Moderately to severely immune compromised* due to a medical condition or receipt of immunosuppressive medications or treatments AND may not mount an adequate immune response to COVID-19 vaccination, OR b. Unable to receive or complete any available COVID-19 vaccine according to approved/authorized schedule due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or a COVID-19 vaccine component(s).	• Active treatment for solid tumor and hematologic malignancies • Receipt of solid-organ transplant and taking immunosuppressive therapy • Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy) • Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome) • Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) • Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

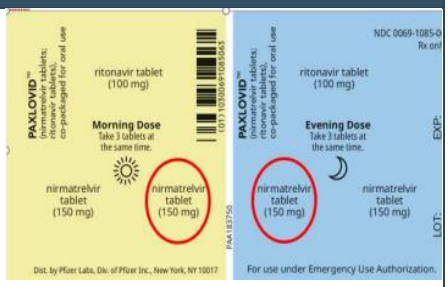
Notes:

- Testing for SARS-CoV-2 by antibody, PCR, or antigen are not required to qualify for pre-exposure prophylaxis.
- PrEP with tixagevimab-cilgavimab is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.
- In individuals who have received a COVID-19 vaccine, tixagevimab-cilgavimab should be administered at least 2 weeks after vaccination.

See ordering information on the Source for outpatient UCHealth infusion sites, patient prioritization, and instructions.

Nirmatrelvir/ritonavir (Paxlovid; Pfizer)

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 protease (Mpro) which subsequently inhibits SARS-CoV-2 replication. Ritonavir is used a pharmacokinetic enhancer to increase the concentrations and half-life of nirmatrelvir. In a trial of non-hospitalized high-risk adults with COVID-19, Paxlovid reduced the risk of hospitalization or death by 89% compared to placebo.



Indication:

- EUA granted for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive SARS-CoV-2 test, and who are at high risk for progression to severe COVID-19, within 5 days of symptom onset.

Dosing:

- 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily without regard to food for 5 days. *Paxlovid is NOT authorized for use >5 consecutive days.*
- Renal and Hepatic Dosage Adjustment:
  - eGFR ≥30-60 mL/min: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily without regard to food for 5 days.
  - No adjustment for patients with mild-moderate liver disease (Child-Pugh Class A or B)
  - For patients with severe renal (eGFR < 30 mL/min) or liver (Child-Pugh Class C) impairment, Paxlovid is not recommended due to lack of pharmacokinetic and safety data in these patient populations.

Pregnancy and Lactation:

- There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production.
- The Society of Maternal-Fetal Medicine issued a statement supporting Paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) use for treating pregnant patients with COVID-19 who meet clinical qualifications. Any therapy that would otherwise be given should not be withheld specifically due to pregnancy or lactation. Consider discussion with Maternal-Fetal Medicine or OB-GYN provider if questions.

Drug Interactions:

- As Paxlovid contains ritonavir, a strong CYP3A4 inhibitor, and nirmatrelvir is a CYP3A4 substrate, the drug is subject to many drug interactions. Below is a list of contraindicated medications as determined by the FDA. A more comprehensive list for commonly encountered medications is available in Appendix A. However, neither list encompasses all possible interactions and are not a substitute for clinical judgment.
- Interactions should always be checked with two sources. The Univ. of Liverpool COVID-19 Interaction Checker is a great reference.
- Please see the UCHealth Paxlovid drug interaction guide in Appendix A for additional tips on managing drug interactions.

Contraindicated Medications	
CYP3A Substrates	**CYP3A4 Inducers**
• Alpha1-adrenoreceptor antagonist: alfuzosin • Analgesics: pethidine, piroxicam, propoxyphene • Antianginal: ranolazine • Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine • Anti-gout: colchicine • Antipsychotics: lurasidone, pimozide, clozapine • Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine • Sedative/hypnotics: triazolam, oral midazolam • Calcineurin inhibitors (e.g., tacrolimus, cyclosporine) • mTOR-inhibitors (e.g., everolimus, sirolimus)	• Anticancer drugs: apalutamide • Anticonvulsant: carbamazepine, phenobarbital, phenytoin • Antimycobacterials: rifampin • Herbal products: St. John's Wort (hypericum perforatum) • HMG-CoA reductase inhibitors: lovastatin, simvastatin • PDE5 inhibitor: sildenafil (Revatio®) used for pulmonary arterial hypertension (PAH)

HIV Considerations:

- There may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. Use caution in persons living with HIV who are not on treatment or in whom HIV replication is not adequately suppressed.
- There are no significant interactions with the commonly prescribed ART regimens: Biktarvy, Descovy + Tivicay, Triumeq, Dovato, Delstrigo, and Symtuza. Monitor for increased side effects with concomitant protease inhibitor regimens.

Molnupiravir (Lagevrio; Merck)

Molnupiravir is an oral antiviral that was granted EUA for the treatment of mild-moderate COVID-19 in adult patients. It is a prodrug converted to N4-hydroxycytidine (NHC) that is subsequently tri-phosphorylated intracellularly to its pharmacologically active triphosphate (NHC-TP). NHC-TP is incorporated into SARS-CoV-2 RNA by RNA polymerase resulting in inhibition of viral replication. In a clinical trial of adults with at least one risk factor for disease progression, treatment with Molnupiravir reduced all-cause hospitalization or death at day 29 compared to placebo (6.8% vs 9.7%, respectively).

Indication:

- Granted EUA for treatment of adult patients with mild-moderate COVID-19, with positive SARS-CoV-2 testing (SARS-CoV-2) viral testing who are high risk for progression to severe COVID-19 and whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate and are within 5 days of symptom onset.
- Molnupiravir is not indicated for patients <18 years old due to concerns for bone and cartilage growth.

Dosing: 800 mg (four capsules) every 12 hours for 5 days, given without regard to food. *Molnupiravir is NOT authorized for use >5 consecutive days*. No adjustment required for renal or hepatic impairment.

Pregnancy and Lactation:

- Molnupiravir is not recommended during pregnancy. Based on animal studies, molnupiravir may cause fetal harm when administered during pregnancy. In women of childbearing age, pregnancy testing should be performed, if indicated, prior to initiating treatment with molnupiravir. Individuals of childbearing potential should use contraception:
    - Females: Individuals of childbearing potential should use contraception during the duration of treatment and for 4 days after the last dose molnupiravir.
    - Males: Sexually active individuals with partners of childbearing potential should use contraception during treatment and for at least 3 months after last dose of molnupiravir.
- Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding or may pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.
- Consider discussion with Maternal Fetal Medicine or OB-GYN provider if questions.

Drug-drug Interactions:

- No drug interactions have been identified based on the limited available data. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted.

Remdesivir (Veklury; RDV)

Remdesivir is FDA-approved for COVID-19 treatment requiring hospitalization in adults and pediatrics (≥12 years and ≥40 kg). Data from the PINETREE study also demonstrates that early RDV in non-hospitalized patients results in significantly fewer COVID-19 related hospitalizations or death at 28-days (0.7% vs. 5.3%, HR 0.13; 95% CI: 0.03-0.59).

Criteria for use:

1. Confirmed COVID-19 by SARS-CoV-2 PCR
2. Symptom duration ≤7 days (may consider longer symptom duration among hospitalized patient who have history of transplantation or moderate-severe immunocompromised status)
    - **Hospitalized patients** requiring supplemental oxygen (see dosing below). Greatest benefit has been shown in those requiring low-flow O2. Patients requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and/or ECMO at baseline are unlikely to benefit from RDV based on current evidence. May continue RDV if patient progresses to mechanical ventilation or ECMO.
    - **Non-hospitalized patients or those hospitalized for other reasons with inadvertent COVID-19 diagnosis** with mild-moderate symptoms of COVID-19, not requiring supplemental O_2, who are at high-risk for disease progression (see dosing below)
3. ALT <10x ULN

Dosing:

- Hospitalized COVID-19 requiring supplemental O_2: 200mg IV on day 1, then 100mg daily on days 2-5 or until discharge.
- Mild-moderate COVID-19 meeting above criteria: 200mg IV on day 1, then 100mg daily on days 2-3.

Ordering and monitoring:

- Monitor LFTs daily. Consider discontinuation if ALT >10x ULN.
- Renal impairment (including CrCl < 30 mL/min and renal replacement therapy) is not a contraindication to RDV. The package insert recommends avoiding use when CrCl <30 mL/min due to cyclodextrin accumulation. However, given the small amount of cyclodextrin and short duration of exposure, adverse events are unlikely and there have been no increased risk of safety events observed in studies.

Approval:

- At UCHealth AMC, RDV is a tier-2 protected antimicrobial (approval by unit pharmacist if criteria are met). Requests not meeting criteria can be made via the Antimicrobial Stewardship secure chat group to "AMC Antimicrobial Stewardship."

Dexamethasone

Dexamethasone is indicated in patients requiring supplemental O_2 for COVID-19, including mechanical ventilation or ECMO. It is NOT recommended in those not requiring supplemental O2.

Dose: 6 mg IV or PO per day

Duration: 10 days, or until hospital discharge. If patient requires a brief hospitalization and still requiring increased oxygen support, consider discharging to complete a 5–7-day course. Alternative glucocorticoids can be considered if dexamethasone is unavailable:

- Prednisone 40 mg per day
- Methylprednisolone 32 mg per day (once daily or 2 divided doses)
- Hydrocortisone 160 mg per day (2-4 divided doses)

Note: Recommend consultation with Maternal Fetal Medicine regarding the use of steroids in pregnant patients.

Tocilizumab (Actemra)

Tocilizumab is an IL-6 receptor antagonist used for treatment of rheumatoid arthritis and cytokine-release syndrome associated with CAR-T cell therapy. It had prior mixed results for COVID-19 treatment, but two recent trials (REMAP-CAP, RECOVERY) suggest a mortality benefit when used **with corticosteroids** in a select population of hospitalized patients who are exhibiting rapid respiratory decompensation.

Indication: Adjunctive therapy to steroids for patients who are recently admitted (hospitalization <3 days) and are:

- Newly admitted to the ICU (within 24hr) with high O2 need (HFNC FiO2 >0.4/flow rate 30L/min, NIV, MV)
- Not yet admitted to ICU but with rapidly increasing O2 need requiring HFNC or NIV, AND have significantly elevated inflammatory markers (CRP >= 75 mg/L)

Dosing: 8mg/kg x 1 dose, rounded as below. Unclear benefit of additional doses.

Weight (kg)	IV Dose	SubQ Pen Formulation Dose
40-65	400 mg	324 mg
66-90	600 mg	648 mg
> 90 kg	800 mg	810 mg

Other considerations:

- Consider assessing response to corticosteroids (e.g., ~48 hours) prior to initiation of tocilizumab
- Tocilizumab has not been shown to provide benefit for patients requiring mechanical ventilation beyond newly intubated patients (<24 hours of mechanical ventilation)
- Tocilizumab should be AVOIDED in:
    - Severely immunocompromised hosts
    - Suspected or confirmed other bacterial, fungal, or viral infection
    - AST/ALT >5x ULN
    - ANC <500, platelets <50K
    - High risk for GI perforation
    - Pregnancy: risk vs. benefit, recommend consultation with Maternal Fetal Medicine
- Monitor for development of new, or re-activation of latent, infections
- Consider screening for latent infections depending on risk factors (e.g., TB, strongyloidiasis, others)
- Consider prophylactic treatment with ivermectin in patients from strongyloides-endemic areas
- Monitor following tocilizumab administration: neutrophils, platelets, LFTs

Baricitinib (Olumiant)

Baricitinib is an oral Janus kinase (JAK) inhibitor that is used for rheumatoid arthritis treatment (non-formulary at UCH). Some data has shown improved time to recovery when given with RDV (ACTT-2, Dec 2020), and lower 28-day all-cause mortality when given with either dexamethasone or dexamethasone + RDV) in patients requiring supplemental oxygen or high-flow/NIV. The benefit of Baricitinib in this trial was most pronounced among those requiring HFNC/NIV at baseline. (COV-BARRIER, May 2021 pre-print). In the subset of critically ill patients requiring mechanical ventilator or ECMO at baseline demonstrated reductions in 28-day all-cause mortality.

Based on these data, the NIH Guideline recommends that for hospitalized patients on high-flow oxygen or NIV who have evidence of clinical progression or increased markers of inflammation, may use either:

- Baricitinib OR tocilizumab plus dexamethasone alone, or
- Baricitinib OR tocilizumab plus dexamethasone + remdesivir
- In circumstances where corticosteroids cannot be used, Baricitinib + RDV can be used for hospitalized, non-intubated patients requiring supplemental O2

Indication

At UCH, Baricitinib will be the preferred adjunctive immunomodulatory therapy to dexamethasone for COVID-19 patients who are:

- Hospitalized < 72 hours
- Experience worsening respiratory function despite dexamethasone who require HFNC or NIV, MV, or ECMO
- Persistently elevated/increasing C-reactive protein

Dosing

- 4 mg once daily x 14 days (may discontinue use before 14 days if patient has recovered and is discharging)
    - Do not continue after hospital discharge

Renal Dosing	
eGFR (mL/min/1.73m^2)	**Dose**
> 60	4 mg daily
30-59	2 mg daily
15-29	1 mg daily or 2 mg q48h
< 15	Contraindicated, hold, and resume once eGFR > 15
Renal Replacement Therapy (IHD, CRRT)	Contraindicated

- Management of Hematologic Abnormalities:
    - ALC < 200: hold Baricitinib, may resume once ALC > 200
    - ANC < 500: hold Baricitinib, and resume once ANC > 500
- Increase in AST or ALT to >5-10x ULN concerning for DILI: hold dose until diagnosis of DILI is excluded

Other considerations:

- Consider assessing response to corticosteroids (e.g., 48 hrs) prior to deciding whether Baricitinib is needed
- Baricitinib should be AVOIDED in:
    - Any form of renal replacement therapy
    - Known active tuberculosis (routine QuantiFERON screening not required if no epidemiologic risk factors)
    - Hemoglobin < 8 g/dL
    - Pregnancy: risk vs. benefit, recommend consultation with Maternal Fetal Medicine
- Screen for drug-drug interactions
- Monitor CBC and BMP daily, LFTs weekly, and for development of new, or re-activation of latent, infections

Appendix A: Nirmatrelvir/Ritonavir (Paxlovid) Interaction Table

Concomitant Medication	Interaction Category	Mechanism	Effect on concentration	Comments
Abemaciclib	D	CYP3A4	↑ abemaciclib	• Co-administration with strong CYP3A4 inhibitors may increase abemaciclib up to 2.5-fold. Use caution and consider dose reduction in consultation with patients oncologist. • Abemaciclib prescribing information states that in patients taking abemaciclib at a dose of 200 mg twice daily or 150 mg twice daily, the abemaciclib dose should be reduced to 100 mg twice daily when combined with strong CYP3A4 inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, a further abemaciclib dose reduction to 50 mg twice daily is recommended when combined with strong CYP3A4 inhibitors. The abemaciclib may be increased back to prior dose 2 days after stopping nirmatrelvir/ritonavir.
Alfuzosin	X	CYP3A4	↑ apixaban	• Co-administration may increase alfuzosin concentrations leading to hypotension.
Alprazolam	C	CYP3A4	↑ alprazolam	• Increased alprazolam exposure and potential side effects may occur. • When combined with nirmatrelvir/ritonavir, consider a lower dose of alprazolam used cautiously and monitor for adverse effects. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 2 days.
Amiodarone	X	CYP3A4	↑ amiodarone	• Coadministration is contraindicated due to increased plasma concentrations of amiodarone. Thereby, increasing the risk of arrhythmias or other serious adverse reactions.
Amlodipine	C	CYP3A4	↑ amlodipine	• Increased amlodipine concentrations up to 2-fold are expected with nirmaltrelvir/ritonavir co-administration. • Reduce amlodipine dose by 50% during coadministration with nirmatrelvir/ritonavir and for a further 2 days after the last dose of nirmatrelvir/ritonavir. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 2 days.
Apalutamide	X	CYP3A4	↓ nirmatrelvir	• Apalutamide is a strong CYP3A4 inducer, and coadministration will significantly lower nirmatrelvir exposure. This may result in loss of antiviral effect and resistance.
Apixaban	X	CYP3A4 P-gP	↑ apixaban	• Apixaban label does not recommend concomitant use with strong dual CYP3A4 and P-gp inhibitors. • High levels of inflammation as observed in some COVID-19 patients can inhibit CYP3A4 and P-gP, therefore increasing magnitude of the interaction. • Management of this interaction should also take into account the indication for anticoagulation and whether or not apixaban can be stopped during the course of nirmatrelvir/ritonavir treatment. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, anticoagulant treatment would have to be resumed 2 days after the last dose of nirmatrelvir/ritonavir.
Atazanavir +/- RTV or Cobi	C	CYP3A4	↑ Atazanavir	• No dosage adjustment indicated, monitor patients for increased side effects (e.g. stomach upset with higher ritonavir dose)
Atorvastatin	D	CYP3A4	↑ atorvastatin	• Coadministration expected to increase atorvastatin exposure 2-3-fold • Given short duration of nirmatrelvir/ritonavir, consider temporary discontinuation of atorvastatin during treatment and resume atorvastatin 2 days after stopping nirmatrelvir/ritonavir.
Bedaquiline	D	CYP3A4	↑ Bedaquiline	• Due to the risk of bedaquiline related adverse events, coadministration should be avoided. • If coadministration is necessary, clinical monitoring including ECG assessment and monitoring of transaminases is recommended. • Consider delaying the next due dose of bedaquiline if it falls during nirmatrelvir/ritonavir treatment until after nirmatrelvir/ritonavir treatment has been completed.

Betrixaban	D	P-gP	↑ Betrixaban	• The US product label for betrixaban recommends for patients receiving or starting a strong P-gp inhibitor to reduce betrixaban dose and use an initial dose of 80 mg followed by 40 mg once daily. • Coadministration of betrixaban might need to be reconsidered in patients with concomitant renal impairment (creatinine clearance less than 60 ml/ml) as renal impairment increases betrixaban exposure. • he management of this interaction should also take into account the indication of the anticoagulation and whether or not betrixaban can be stopped during the course of nirmatrelvir/ritonavir treatment. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, anticoagulant treatment would have to be resumed 2 days after the last dose of nirmatrelvir/ritonavir.
Bosentan	X	CYP3A4 OAT1B1/3	↑ bosentan	• Lopinavir/ritonavir increased bosentan AUC 48-fold.
Budesonide – inhaled	C	CYP3A4	↑ budesonide	• Systemic exposure from inhaled budesonide increased significantly with concurrent strong CYP3A4 inhibitors leading to Cushing's risk. • Its unclear if the short-term exposure from 5 days nirmatrelvir/ritonavir would lead to clinically significant risk. • May consider switch to alternative inhaled glucocorticoid (e.g. beclomethasone).
Buspirone	D	CYP3A4	↑ buspirone	• Significant increase in buspirone exposure has been demonstrated with other strong CYP3A4 inhibitors. Caution should be taken with coadministration and empiric reduction of buspirone dose to 2.5mg daily during and for 2 days after treatment with nirmatrelvir/ritonavir
Carbamazepine	X	CYP3A4	↓ nirmatrelvir	• Significant reduction in nirmatrelvir AUC observed (55%) with carbamazepine coadministration, which could result in antiviral failure and resistance.
Cisapride	X	CYP3A5	↑ cisapride	• Increase cisapride concentrations may result in serious and/or life-threatening reactions such as cardiac arrhythmias.
Clarithromycin	D	CYP3A4	↑ clarithromycin	• Coadministration with ritonavir increases clarithromycin AUC 77%. • Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. • Clarithromycin doses greater than 1 gr per day should not be coadministered with ritonavir. • Product labels recommend a dose reduction of clarithromycin for patients with impaired renal function (Clcr 30-60 mL/min, dose reduce clarithromycin by 50%; CLcr less than 30 mL/min, dose reduce clarithromycin by 75%).
Ceritinib	D	CYP3A4	↑ ceritinib	• Coadministration should be avoided when possible. If combined, the ceritinib dose should be reduced by approximately one-third (to the nearest 150 mg). Two days after Paxlovid is discontinued, the prior ceritinib dose should be resumed.
Clobazam	D	CYP3A4 CYP2C19	↑ clobazam	• CYP3A4 inhibition by nirmatrelvir/ritonavir may increase clobazam exposure and prolong the duration of its effect, whereas induction of CYP2C19 by ritonavir may decrease N-desmethylclobazam. The net effect of these interactions is unknown. • Use with caution, consider dose reduction and monitor for adverse effects. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory is predicted to mostly disappear after 2 days.
Clonazepam	C	CYP3A4	↑ clonazepam	• Inhibition of CYP3A4 by ritonavir may increase clonazepam concentrations and a decrease in dose may be necessary
Clopidogrel	D	CYP3A4	↓ clopidogrel active metabolite	• Platelet inhibition was also assessed and significantly impaired with concurrent ritonavir, decreasing from 42% to 4% inhibition. • The management of this interaction requires to take into account whether or not a transient loss of clopidogrel efficacy during the short duration of nirmatrelvir/ritonavir treatment is acceptable. The initial 6 weeks post coronary stenting represents a high risk situation which does typically warrant a transition to prasugrel

Clozapine	X	CYP3A4	↑ Clozapine	• Coadministration is contraindicated due to increased clozapine plasma concentrations, which may result in serios hematologic effects.
Colchicine	X	CYP3A4 P-gP	↑ colchicine	• Ritonavir significantly increased colchicine Cmax and AUC by 2.7-fold and 3.5-fold, which may result in serios side effects.
Cyclosporine	X	CYP3A4	↑ cyclosporine	• Management of this interaction is challenging and would require dosage adjustment and therapeutic drug monitoring of cyclosporin which may not be possible given the short duration of nirmatrelvir/ ritonavir treatment. An alternative COVID treatment may need to be considered.
Dabigatran	C	P-gP	↓ dabigatran	• Coadministration of dabigatran (150 mg single dose either 2 hours before or simultaneously with ritonavir), and no statistically significant changes to dabigatran AUC or Cmax when administered simultaneously with ritonavir. However, when administered 2 hours apart the AUC decreased 29%. No change in thrombin time was noted in either arm. • It is recommended to administer nirmatrelvir/ritonavir simultaneously with dabigatran. Caution/not recommended to coadminister with moderate renal impairment.
Dasatinib	D	CYP3A4	↑ dasatinib	• Coadministration should be avoided, however if required dasatinib dose reduction is recommended with monitoring for side effects.
Diazepam	D	CYP3A4	↑ diazepam	• Increased risk of extreme sedation and respiratory depression. If co-administration is deemed essential, use with caution, consider dose reduction and monitor for adverse effects.
Digoxin	D	P-gP	↑ digoxin	• Caution should be exercised when co-administering Paxlovid with digoxin, with appropriate monitoring of serum digoxin levels.
Diltiazem	D	CYP3A4	↑ diltiazem	• If coadministered, monitor for side effects such as hypotension, flushing, and oedema, and, if necessary, a reduction of diltiazem dose should be considered. CYP3A4 inhibition is expected to mostly disappear 2 days after stopping Paxlovid.
Disopyramide	X	CYP3A4	↑ disopyramide	• Coadministration may increase disopyramide exposure and thereby the risk of cardiac arrhythmias
Dofetilide	X	CYP3A4	↑ dofetilide	• Coadministration could potentially increase dofetilide exposure and thereby increase the risk of cardiac arrhythmias.
Doxazosin	C	CYP3A4	↑ doxazosin	• Increased doxazosin exposure may result in hypotension. • Patients should be advised to monitor for signs or symptoms of hypotension. • Given the short duration of Paxlovid, no dose adjustment is recommended, but consider stopping doxazosin for the remainder of the Paxlovid course if symptomatic hypotension occurs.
Dronedarone	X	CYP3A4	↑ dronedarone	• Dronedarone AUC increased 17-fold with other strong CYP3A4 inhibitor coadministration, which increases risk for serious side effects.
Edoxaban	D	P-gP	↑ edoxaban	• Given the short duration of nirmatrelvir/ritonavir treatment, coadministration is possible. US product label recommends no dose modification. Monitor for signs/symptoms of bleeding.
Elbasvir/ Grazoprevir	X	OATP1B	↑ elbasvir and grazoprevir	• Co-administration may increase elbasvir and grazoprevir concentrations. Increased grazoprevir concentrations can result in ALT elevations.
Eplerenone	X	CYP3A4	↑ eplerenone	• Eplerenone exposure increased significantly (up to 4-fold), which may increase risk for hyperkalemia and hypotension.
Everolimus	X	CYP3A4	↑ everolimus	• Coadministration with other strong CYP3A4 inhibitors increased everolimus exposure 15-fold. Coadministration is not recommended.
Fentanyl	D	CYP3A4	↑ fentanyl	• Could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Coadministration may require dosage adjustment and requires careful monitoring of therapeutic and adverse effects including potentially fatal respiratory depression.

Flecainide	X	CYP3A4	↑ flecainide	• Elevated plasma concentrations of flecainide may lead to serious or life-threatening adverse effects and concurrent use is contraindicated.
Glecaprevir/ Pibrentasvir	X	OATP1B1 P-gP	↑ glecaprevir and pibrentasvir	• Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Glimepiride	C	CYP2C9	↓glimepiride	• Not specifically studied. Ritonavir is a weak CYP2C9 inducer, which may lower glimepiride exposure. Given the short duration of Paxlovid the interactions is unlikely clinically significant.
Glipizide	C	CYP2C9	↓glipizide	• Not specifically studied. Ritonavir is a weak CYP2C9 inducer, which may lower glipizide exposure. Given the short duration of Paxlovid the interactions is unlikely clinically significant.
Glyburide	C	CYP3A4	↑ glyburide	• Monitor blood sugar levels at home. After stopping Paxlovid, the inhibitory effects should dissipate in 2 days.
Haloperidol	C	CYP2D6	↑ haloperidol	• The potential limited increase in haloperidol exposure is not expected to increase the risk of QT interval prolongation. • No empiric dose adjustment is recommended, however, careful monitoring of adverse effects is advised.
Hydrocodone	C	CYP3A4 CYP2D6	↑ hydrocodone	• Inhibition of CYP3A4 and CYP2D6 by nirmatrelvir/ritonavir may increase hydrocodone concentrations but decrease concentrations of norhydrocodone and hydromorphone. The clinical significance of this is unclear. Monitor the analgesic effect and sign of opiate toxicity.
Hydromorphone	C	UGT	↓ hydromorphone	• Potential to decrease analgesic effect, advise patients to contact prescriber in case of reduced analgesic effect. Assess for risk of loss of pain control and/or withdrawal to determine if dose adjustment or alternative necessary.
Hydroxyzine	C	CYP3A4	↑ hydroxyzine	• Coadministration may lead to increased hydroxyzine exposure and sedation risk. Advise patients about risk for excess sedation.
Isavuconazole	C	CYP3A4	↑isavuconazole	• Given its safety profile and short duration with Paxlovid, no dose adjustment advised. Monitor for increased side effects with isavuconazole.
Itraconazole	C	CYP3A4	↑itraconazole	• Careful monitoring of therapeutic and adverse effects is recommended when itraconazole is coadministered with ritonavir.
Ivabradine	X	CYP3A4	↑ ivabradine	• Coadministration is likely to increase ivabradine concentrations which may be associated with the risk of excessive bradycardia.
Ivermectin	D	CYP3A4 P-gP	↑ ivermectin	• Increases ivermectin exposure and may increase transfer across blood-brain barrier leading to increased neurotoxicity risks. Paxlovid inhibition should dissipate 2-days after end of therapy. If ivermectin needed, assess risk/benefit for concurrent therapy vs. delayed start until 2-days after Paxlovid completed.
Ketoconazole	D	CYP3A4	↑ ketoconazole	• Ritonavir increased ketoconazole AUC and Cmax by 3.4-fold and 55%. • Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered
Lovastatin	X	CYP3A4	↑ lovastatin	• Coadministration is contraindicated due to increased plasma concentrations of lovastatin; thereby, increasing the risk of myopathy including rhabdomyolysis. • Given the short duration of Paxlovid treatment, lovastatin should be stopped 12 hours before first dose of Paxlovid, and restarted 2 days after the last dose of Paxlovid.
Lurasidone	X	CYP3A4	↑	• Use is contraindicated due to increased risk for side effects.
Methadone	C	CYP2B6 CYP3A4	↓ methadone	• Coadministration with ritonavir decreased methadone AUC and Cmax by 36% and 38%. Monitor for signs/symptoms of withdrawal, and Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
Midazolam	X	CYP3A4	↑ midazolam	• Coadministration of nirmatrelvir/ritonavir and PARENTERAL midazolam should be done with caution and in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for PARENTERAL midazolam should be considered, especially if more than a single dose of midazolam is administered

Mirtazapine	C	CYP3A4	↑ mirtazapine	• Coadministration with ketoconazole (a potent CYP3A4 inhibitor) increased mirtazapine Cmax and AUC by ~40 % and ~50%. Use with caution as mirtazapine has been shown to prolong the QT interval
Morphine	D	UGT P-gP	↓ morphine ↑ morphine-6G	• Monitor for signs of excess sedation and respiratory depression.
Nifedipine	D	CYP3A4	↑ nifedipine	• Caution is warranted, and if coadministered, monitor for side effects such as hypotension, flushing, and oedema. If necessary, a reduction of nifedipine dose should be considered.
Nilotinib	D	CYP3A4	↑ nilotinib	• Coadministration should be avoided. If necessary, nilotinib dose reduction to 300mg once daily for patients with resistant or intolerant Ph+ CML, or to 200 mg once daily for patients with newly diagnosed Ph+ CML in chronic phase is recommended with close monitoring for side effects including QTc prolongation.
Oxcarbazepine	B	CYP3A34	↓ nirmatrelvir	• Oxcarbazepine is a moderate CYP3A4 inducer and could potentially decrease nirmatrelvir exposure, although to a limited extent. Combined with darunavir and twice daily ritonavir, darunavir levels only reduced 10%. Interaction unlikely clinically-relevant.
Oxycodone	C	CYP3A4	↑ oxycodone	• A dose reduction of oxycodone may be required to prevent opioid-related adverse effects with clinical monitoring. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect is predicted to mostly disappear after 2 days.
Phenobarbital	X	CYP3A4	↓ nirmatrelvir	• Significantly reduced nirmatrelvir plasma concentrations may be associated with loss of virologic response and resistance. • Paxlovid cannot be started immediately after discontinuation of phenobarbital due to the delayed offset of CYP3A induction.
Phenytoin	X	CYP3A4	↓ nirmatrelvir	• Significantly reduced nirmatrelvir plasma concentrations may be associated with loss of virologic response and resistance. • Paxlovid cannot be started immediately after discontinuation of phenytoin due to the delayed offset of CYP3A induction.
Piroxicam	X	?	↑ piroxicam	• Contraindicated in EUA document due to potential for increased concentrations leading to respiratory depression or hematologic effects. Mechanism not clear.
Posaconazole	C	CYP3A4	↑nirmatrelvir	• Monitor for side effects associated with Paxlovid.
Primidone	X	CYP3A4	↓ nirmatrelvir	• Significantly reduced nirmatrelvir plasma concentrations may be associated with loss of virologic response and resistance. • Paxlovid cannot be started immediately after discontinuation of primidone due to the delayed offset of CYP3A induction.
Propafenone	X	CYP2D6 CYP3A4	↑ propafenone	• Increased risk of arrhythmias or other serious adverse reactions.
Quetiapine	X	CYP3A4	↑ quetiapine	• Coadministration is contraindicated due to increased plasma concentrations of quetiapine which may lead to coma.
Quinidine	X	CYP3A4	↑ quinidine	• Increased risk of arrhythmias or other serious averse effects.
Ranolazine	X	CYP3A4	↑ ranolazine	• Increased risk for serious and/or life-threatening reactions.
Repaglinide	C	CYP3A4	↑ repaglinide	• Advise patients to monitor blood glucose levels at home. Dose adjustment may be needed. CYP3A4 inhibitory effects expected to wear off 2 days after stopping Paxlovid.
Rifabutin	D	CYP3A4	↑ rifabutin	• Consider reducing rifabutin dose to 150mg daily during Paxlovid treatment and for 2 days after Paxlovid completion once CYP3A4 inhibitory effects wear off, then resume normal rifabutin dosing.
Rifampin	X	CYP3A4	↓ nirmatrelvir	• Significantly reduced nirmatrelvir plasma concentrations may be associated with loss of virologic response and resistance. • Paxlovid cannot be started immediately after discontinuation of rifampin or rifapentine due to the delayed offset of CYP3A induction.
Rifapentine	X	CYP3A4	↓ nirmatrelvir	
Rivaroxaban	X	CYP3A4 P-gP	↑ rivaroxaban	• Increased bleeding risk, coadministration not recommended.

Rosuvastatin	D	?	↑ rosuvastatin	• Rosuvastatin should be stopped temporarily when starting Paxlovid. Restart rosuvastatin 2 days after the last dose of Paxlovid.
Ruxolitinib	D	CYP3A4	↑ ruxolitinib	• Monitor closely for cytopenia and adjust ruxolitinib dosing based on safety and efficacy.
Sildenafil – used for PAH	X	CYP3A4	↑ sildenafil	• Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope.
Simvastatin	X	CYP3A4	↑ simvastatin	• Simvastatin should be stopped when starting Paxlovid. Restart simvastatin 2 days after the last dose of Paxlovid.
Sirolimus	X	CYP3A4	↑ sirolimus	• >10-fold increase in sirolimus, do not coadminister.
Tacrolimus	D	CYP3A4	↑ tacrolimus	• Avoid coadministration, interaction is challenging to manage and requires frequent drug levels and dose adjustments.
Tadalafil – used for PAH	X	CYP3A4	↑ tadalafil	• Co-administration contraindicated due to the potential for tadalafil associated adverse events, including hypotension and syncope.
Tamsulosin	C	CYP3A4	↑ tamsulosin	• Consider max 0.4mg/day and monitor blood pressure closely.
Terazosin	D	CYP3A4	↑ terazosin	• Monitor for hypotension, if symptomatic hypotension occurs consider stopping terazosin for remainder of Paxlovid treatment.
Ticagrelor	X	CYP3A4	↑ ticagrelor	• Increased bleeding risk, prasugrel can be used with Paxlovid unless clinical condition that contraindicates its use.
Triamcinolone	D	CYP3A4	↑ triamcinolone	• Caution with coadministration due to risk for Cushing's syndrome.
Valproate	D	UGT CYP2C9	↓ valproate	• Careful monitoring of valproate serum levels/therapeutic effect.
Valsartan	C	OATP1B1 MRP2	↑ valsartan	• Monitor for signs and symptoms of hypotension
Venetoclax	D	CYP3A4 P-gP	↑ venetoclax	• Coadministration should be avoided when possible, and is contraindicated during the initiation and ramp-up phase.
Verapamil	D	CYP3A4	↑ verapamil	• Use with caution and monitor for increased side effects, such as bradycardia, hypotension or dizziness and, if necessary, a reduction of verapamil dose should be considered.
Vinblastine	C	CYP3A4	↑ vinblastine	• Monitor for increased side effects.
Vincristine	D	CYP3A4	↑ vincristine	• Avoid coadministration if possible. If necessary to coadminister, monitor closely for vincristine toxicities.
Voriconazole	D	CYP2C19	↓ voriconazole	• Coadministration should be avoided unless risk/benefit justifies combination. Voriconazole AUC decreased 39% with ritonavir BID.
Warfarin	D	CYP3A4 CYP2C9	↑/↓ warfarin	• Coadministration not recommended. If necessary, monitor INR closely. Increased risk for bleeding or thrombosis.
Ziprasidone	C	CYP3A4	↑ ziprasidone	• Monitor for adverse effects.
Zolpidem	C	CYP3A4	↑ zolpidem	• Zopidem AUC increased 28%. May be coadministered with carefule monitoring for excessive sedative effects.
Drug interaction category definitions: A=No interation; B=No action needed; C=Monitor therapy; D=Modify regimen; X=avoid combination				