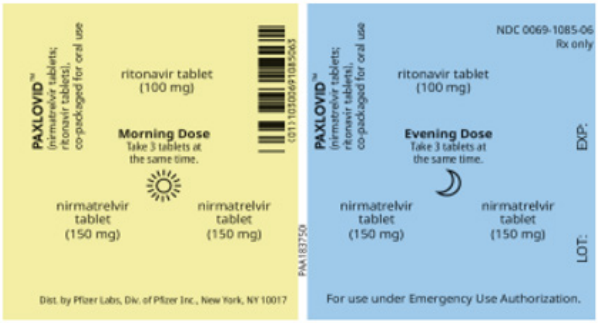
Nirmatrelvir/Ritonavir (Paxlovid™) Point-of-Care Reference

Last reviewed: 1/28/22

Nirmatrelvir/ritonavir (brand name Paxlovid™) has been FDA-authorized for emergency use to treat mild-to-moderate COVID-19 since December 2021.



CLINICAL INFORMATION

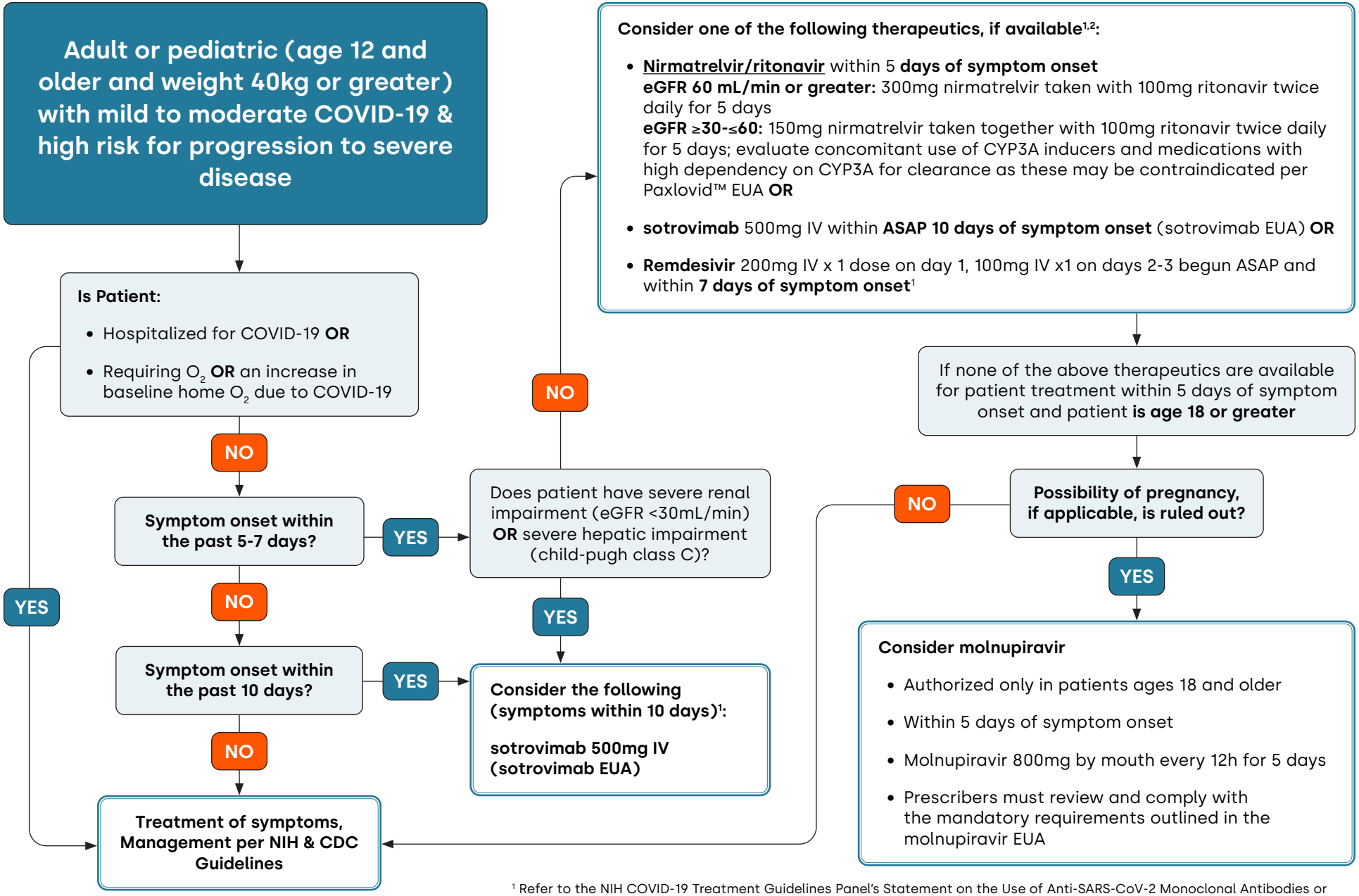
Eligibility: The nirmatrelvir/ritonavir EUA covers adults and pediatric patients 12 years and older weighing at least 40 kg (88 lb) with positive SARS-CoV-2 test results who are at high risk for progression to severe COVID-19. Nirmatrelvir/ritonavir is not recommended for patients with severe renal impairment.

Dosing: Nirmatrelvir/ritonavir is dispensed in blister packs that contain two 150 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir. Nirmatrelvir/ritonavir dosing varies by kidney function, as below, so in some cases, only one of the nirmatrelvir tablets will be needed (a 100 mg ritonavir tablet, however, is always given, regardless of renal function):

EGFR (CKD-EPI formula)	Dose of nirmatrelvir/ritonavir
>60 mL/min	300 mg nirmatrelvir + 100 mg ritonavir, twice daily for 5 days
30≤60 mL/min	150 mg nirmatrelvir + 100 mg ritonavir, twice daily for 5 days
<30 mL/min	Not recommended: Appropriate dosing has not been determined.

Clinical Decision-Making: In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, IDSA guidelines suggest nirmatrelvir/ritonavir be initiated within 5 days of symptom onset (conditional recommendation, low certainty of evidence). NIH guidelines also suggest nirmatrelvir/ritonavir for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk of disease progression.

HHS's COVID-19 Therapeutics Decisionmaking Aid offers a path to evaluate treatment options:



Limited use of bamlanivimab/etesevimab and REGEN-COV as they are not expected to be active against the Omicron variant[1]

[1] Refer to the NIH COVID-19 Treatment Guidelines Panel's Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of Covid-19 in Nonhospitalized patients when Omicron is the Predominant Circulating Variant; Remdesivir is only approved for hospitalized individuals with COVID-19. Outpatient treatment is based on information from the literature (Dec 22, 2021 Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients; DOI: 10.1056/NEJMoa2116846)

[2] COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease in either the outpatient or inpatient setting (COVID-19 Convalescent Plasma EUA)

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Graphic based on COVID-19 therapeutics decision-making aid created by the U.S. Department of Health and Human Services Office of the Assistant Secretary for Preparedness (https://www.phe.gov/emergency/events/COVID19/therapeutics/Documents/COVID-Therapeutics-Decision-Aid.pdf)

NIH's COVID-19 Treatment Guidelines Panel offers a prioritization scheme based on four key elements: age, vaccination status, immune status and clinical risk factors:

Risk Group 1	Immunocompromised individuals 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 (see Immunocompromising Conditions below); or Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
Risk Group 2	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).
Risk Group 3	Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors). **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.
Risk Group 4	Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors). **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.

DRUG-DRUG INTERACTION

Interactions With Other COVID-19 Therapeutics: Nirmatrelvir/ritonavir's inclusion of ritonavir, a protease inhibitor used to boost levels of companion drugs via its inhibition of cytochrome P450 metabolizing enzymes, may in some cases have important implications for other COVID-19 therapeutics (while nirmatrelvir/ritonavir is only authorized for use in nonhospitalized patients, in cases where patients go on to be hospitalized despite nirmatrelvir/ritonavir use, some of these interactions may become relevant):

COVID-19 Therapeutic	Expected Effect of Ritonavir
Dexamethasone	Increased serum concentrations of dexamethasone[1]
Methylprednisolone	Increased serum concentrations of methylprednisolone[1]
Remdesivir	No effect expected[2]
Anti-SARS-CoV-2 Monoclonal Antibodies	No effect expected[3]
Convalescent Plasma	No effect expected[4]
Molnupiravir	No effect expected[5]
Tocilizumab	No effect expected[6]
Baricitinib	No significant effect expected[7]
Ruxolitinib	Ruxolitinib exposures significantly increased; avoid or monitor for toxicities (cytopenias)[8]
Colchicine	AUC colchicine increased 2.5 to 3.5-fold; avoid coadministration[9]

Note: Threshhold of clinical significance was considered to be a >15% impact on drug concentrations, for this table.

[1] Combination has been associated with elevated steroid levels and development of Cushing's syndrome as early as 14 days from the start of coadministration. Given the low doses of dexamethasone used in COVID-19 treatment, this increase in steroid levels may not be clinically significant (University of Liverpool COVID-19 Drug Interactions).

[2] *In vivo* drug-drug interaction studies with remdesivir have not been conducted; *in vitro* studies suggest remdesivir is a substrate of CYP 3A4 (responsible for about 10% of its metabolism) and OATP1B1 and P-gp, but its metabolism is predominantly mediated by hydrolases and carboxylesterases. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.

[3] e.g., Sotrovimab EUA factsheet, FDA (degraded by proteolytic enzymes and not CYP 450 enzymes) https://www.fda.gov/media/149534/download

[4] Convalescent Plasma EUA factsheet https://www.fda.gov/media/141478/download

[5] Molnupiravir is primarily hydrolyzed by esterases and then intracellularly phosphorylated, so DDIs not likely. https://www.fda.gov/media/155054/download

[6] Note that cytokines often have a hepatic inhibitory effect on Cytochrome P450 enzymes, so blocking IL-6 could potentially restore function to these enzymes, though this would be counteracted by the effect of RTV. But tocilizumab is eliminated through binding to its target antigen. Actemra (tocilizumab) FDA Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125276s092lbl.pdf

[7] Less than 10% of baricitinib's metabolism is via cytochrome P450 enzymes, and coadministration with ketoconazole (another strong CYP 3A inhibitor) did not alter concentrations (https://go.drugbank.com/drugs/DB11817; https://ard.bmj.com/content/74/Suppl_2/1063.1).

[8] https://pubmed.ncbi.nlm.nih.gov/31145690/

[9] https://journals.sagepub.com/doi/full/10.4137/CMT.S10561

Other Medications That Are Contraindicated and Should Not Be Coadministered With Nirmatrelvir/Ritonavir: ***NIH*** recommends ***prescribing an alternative COVID-19 therapy for patients receiving any of the medications listed:*** amiodarone, apalutamide, bosentan, carbamazepine, cisapride, clopidogrel, clozapine, colchicine in patients with renal and/or hepatic impairment, disopyramide, dofetilide, dronedarone, eplerenone, ergot derivatives, flecainide, flibanserin, glecaprevir/pibrentasvir, ivabradine, lumateperone, lurasidone, mexiletine, phenobarbital, phenytoin, pimozide, propafenone, quinidine, ranolazine, rifampin, rifapentine, rivaroxaban, sildenafil for pulmonary hypertension, St. John's wort, tadalafil for pulmonary hypertension, ticagrelor or vorapaxar.

NIH recommends ***withholding or substituting if clinically appropriate if the patient is receiving any of these medications*** (if withholding is not clinically appropriate, use an alternative medication): alfuzosin, alprazolam, atorvastatin, avanafil, clonazepam, codeine, cyclosporine, diazepam, everolimus, fentanyl, hydrocodone, lomitapide, lovastatin, meperidine (pethidine), midazolam (oral), oxycodone, piroxicam, propoxyphene, rosuvastatin, salmeterol, sildenafil for erectile dysfunction, silodosin, simvastatin, sirolimusb, suvorexant, tacrolimus, tadalafil for erectile dysfunction, tamsulosin, tramadol, triazolam or vardenafil.

SUPPLY & ACCESS

Distribution: Nirmatrelvir/ritonavir is currently available in limited quantities in the U.S. and is being allocated by the federal government to health departments in states, territories and jurisdictions as well as select community health centers.

For allocation details, refer to HHS's weekly distribution summaries; for information intended for health providers, see HHS's COVID-19 Therapeutics Locator; for provider-specific distribution information, view HHS's COVID-19 Public Therapeutics Locator. Contact your state, territorial or jurisdictional health department for further local information.

CODING, BILLING & REPORTING

Coding:

Drug Name	Dosage	Package Size	NDC
Paxlovid™ EUA	300-100 mg	6 tablets	00069-1085-06
Paxlovid™ EUA	300-100 mg	30 tablets	00069-1085-30

Billing: Paxlovid™ has been added by the Health and Human Services Commission to the Medicaid and Children's Health Insurance Program (CHIP) formularies as a payable pharmacy benefit.

Reporting: Providers are required to report federally purchased course administration daily by 11:59 p.m. ET via HHS's Health Partner Order Portal.

FURTHER INFORMATION

Real-Time Learning Network Paxlovid™ Literature Reviews
FDA Paxlovid™ EUA Fact Sheet for Healthcare Providers
NIH Treatment Guidelines Panel Statement on Potential Drug-Drug Interactions
NIH Treatment Guidelines Panel Statement on Patient Prioritization
HIVMA Considerations for People with HIV and Hepatitis C
University of Liverpool COVID-19 Prescribing Resources
University of Liverpool COVID-19 Drug Interactions