ORAL ANTIVIRALS FOR THE TREATMENT OF COVID-19

This treatment guidance document summarizes two new anti-viral oral medications for treatment of mild to moderate COVID-19 disease: molnupiravir and nirmatrelvir co-packaged with ritonavir (Paxlovid). Both received FDA Emergency Use Authorization (EUA) December 2021. This information is subject to rapid change as more is learned.

At Wellforce, acknowledging significant limitations of available treatment courses, at this time we are prioritizing treatment of COVID-19 in unvaccinated or incompletely vaccinated individuals with clinical risk factors for severe illness and vaccinated individuals who are not expected to mount an adequate immune response.

DRUG	MOLNUPIRAVIR	NIRMALTREVIR/RITONAVIR
Patient population	Age 18+	Age 12+ with weight 40kg+
FDA EUA indication	• Positive SARS-CoV-2 test • Non-hospitalized patients with mild to moderate symptomatic COVID-19 (O2 sat > 93%) with at least one comorbidity* at risk for hospitalization/death ○ If patient is hospitalized for reasons other than COVID, therapy can be continued to complete 5 days, however short course (3 day) remdesivir is preferred • Must be initiated within 5 days of symptom onset • NOT indicated for pre-exposure or post-exposure prophylaxis	
***Comorbidities**	> 65 years old Blood stem cell transplant Cancer Chronic kidney disease Chronic liver disease Chronic lung disease Dementia or other neurological conditions Diabetes Down syndrome Heart Conditions HIV infection Mental Health conditions	Overweight and obese BMI > 25 Pregnancy Sickle cell disease Smoking (current or former) Solid organ transplant Stroke/ Cerebrovascular disease Substance abuse disorder Tuberculosis A full list is available on the CDC website https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
DOSING		
	200 mg, 4 capsules BID x 5 days with or without food	300 mg nirmaltrevir (two 150 mg tablets) plus 100 mg ritonavir BID x 5 days, with or without food
Packaging	Bottle (40 capsules)	Blister Pack (20 tabs)
Renal impairment	No adjustment	eGFR > 60 ml/min: no adjustment eGFR ≥ 30 to <60 mL/min: 150 mg nirmatrelvir and 100 mg ritonavir twice daily eGFR < 30 ml/min: not recommended
Hepatic impairment	No adjustment	OK to use in Childs-Pugh class A,B Class C not recommended as no data

continued

DRUG	MOLNUPIRAVIR	NIRMALTREVIR/RITONAVIR
SIDE EFFECTS		
	Diarrhea (2%) Nausea (1%) Dizziness (1%) Embryo-fetal toxicity (see special populations below) Risk of Bone and Cartilage Toxicity (not approved in patients < 18 yo)	Dysgeusia (6%) Diarrhea (3%) Hypertension (1%) Myalgia (1%) LFT abnormalities
DRUG INTERACTIONS		
	None known at this time	Ritonavir is a potent CYP3A inhibitor See Appendix 1 below
SPECIAL POPULATIONS		
HIV issues	No data; not contraindicated	Patient on current HIV medications containing ritonavir or cobicistat should continue their HIV regimen as usual, no dose adjustment Risk of developing protease inhibitor mutations in patients with uncontrolled or unknown HIV+ status
Females of childbearing potential	Not recommended during pregnancy Recommended to obtain a pregnancy test prior to starting treatment Reliable contraception during treatment and for 4 days after	Ritonavir safe in pregnancy Nirmaltrevir — human studies lacking If using oral contraceptives — need alternative method as ritonavir will inactivate
Lactation	Not recommended during treatment or for 4 days after; "pump and dump"	No data on effects on the breastfed infant
Males of childbearing potential	Reliable contraception during treatment and 3 months after; unknown long term effects on sperm	Not mentioned in EUA
PATIENT FACTSHEET MUST BE PROVIDED WHEN DISPENSING		
	https://www.fda.gov/media/155055/download	https://www.fda.gov/media/155051/download
HEALTHCARE PROFESSIONAL FACTSHEET		
	https://www.fda.gov/media/155054/download	https://www.fda.gov/media/155050/download

MOLNUPIRAVIR

Molnupiravir received FDA EUA on 12/23/21 for treatment of mild to moderate COVID-19 in people age 18+ years who are at high risk of hospitalization or death. Its mechanism of action is RNA-dependent RNA polymerase inhibitor via "Error Catastrophe Method" (Kabinger 2021). Molnupiravir is a prodrug of N-hydroxycytosine (NHC), which is phosphorylated intracellularly to NHC triphosphate (NHC-TP). NHC-TP is then incorporated into viral RNA via viral polymerase, resulting in errors in the viral genome that prohibit viral replication.

Notable: The prodrug NHC has mutagenicity as well as fetal toxicity concerns.

NHC is mutagenic to mammalian cells; mutagenic ribonucleoside analogs can also enter the pathway to form DNA; ribonucleoside form of NHC able to cause mutations in a lung carcinoma cell line at low concentrations. Also theoretical concern exist that NHC could introduce mutations into virus, or cause birth defects. Genotoxicity studies by drug sponsor demonstrate it is mutagenic in some bacteria and a pig assay but not in a rat assay. (Zhou 2021; Haseltine 2021)

Phase 3 Clinical Trial (P002): MOVe-OUT Study

In a multicenter placebo-controlled RCT (1:1 randomization), nonhospitalized, nonvaccinated adults age 18+ with at least one risk factor for severe COVID-19 were given molnupiravir 800 mg PO twice per day vs placebo x 5 days, randomized within 5 days of onset of symptoms for PCR-proven COVID-19.

Inclusions: unvaccinated and nonhospitalized adults age 18+ years with mild to moderate COVID-19 (PaO2 > 93%); randomized within 5 days of PCR-proven symptomatic disease; at least one risk factor for progression to severe disease (obesity, an age of over 60 years, diabetes, and heart disease, etc.)

Exclusions: Exclusion criteria included currently hospitalized or expected to need hospitalization for COVID-19 within 48 h of randomization, on dialysis, or having reduced estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 by the Modification of Diet in Renal Disease (MDRD) equation, having any of the following conditions: human immunodeficiency virus (HIV), history of hepatitis B virus (HBV) or hepatitis C virus (HCV) with cirrhosis, end-stage liver disease, hepatocellular carcinoma, aspartate aminotransferase (AST) and/or ALT) >3X upper limit of normal and low platelet count <100,000/μL. (Bernal et al 2021; reviewed in Singh 2021).

Primary endpoint: Percentage of patients hospitalized or who died through day 29. Preplanned interim analysis when 50% of participants completed day 29 (n=775) which showed approximate 50% reduction in hospitalization or death with treatment. Therefore trial stopped as recommended by DMC (Data Monitoring Committee) in consultation with FDA. In the full population analysis, hospitalization and death were lower in the molnupiravir arm compared to placebo (6.8% vs 9.7%;, RR 31%). Molnupiravir has been approved for use in UK.

Study findings — Interim analysis: risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). Adverse events were very similar on the two groups (216/710 participants (30.4%) in the molnupiravir group and 231/701 (33.0%) in the placebo group. (Bernal 2021).

NIRMALTREVIR/RITONAVIR (PAXLOVID)

Nirmaltrevir/ritonavir received FDA EUA 12/22/21 for treatment of mild to moderate COVID-19 in people age 12+ years weighing 40 kg or more who are at high risk of hospitalization or death. The mechanism of action of nirmaltrevir is a selective viral protease inhibitor. SARS-CoV-2 genome encodes two polyproteins essential for viral replication. They need to be cleaved into functional proteins by a viral protease so this action is blocked by nirmaltrevir. Because nirmaltrevir is metabolized by CYP3A4 enzymes, ritonavir can boost nirmaltrevir's plasma levels becauase ritonavir is a potent CYP3A4 inactivator. Ritonavir has no activity against SARS-CoV-2.

Notable. High risk of clinically significant drug interactions.

Boosting with ritonavir is the same strategy employed in HIV treatment, where HIV-targeted protease inhibitors' plasma levels are boosted by ritonavir. This strategy has drug interaction implications where there are many drugs that may have dangerously raised or lowered serum levels due to ritonavir's inhibition of CYP3A4. Every concomitant medication must be checked for drug interactions. Please see Appendix 1 for a list of drug interactions.

EPIC-HR study (NCT04960202)

In a multicenter placebo-controlled RCT (1:1 randomization), nonhospitalized, nonvaccinated adults age 18+ with at least one risk factor for severe COVID-19 were given nirmaltrevir 300 mg (two 150 mg tablets) and one 100 mg ritonavir tablet PO twice per day vs placebo x 5 days, randomized within 5 days of onset of symptoms for PCR-proven COVID-19.

Inclusions: unvaccinated nonhospitalized adults age 18+ years with mild to moderate COVID-19 s/s (O2 saturation >93%) and confirmed SARS-CoV-2 infection within 5 days prior to randomization. At least one characteristic or underlying medical condition associated with increased risk of severe illness from COVID-19 (diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities).

Exclusions: related to COVID-19: prior COVID-19 vaccination, prior disease, prior convalescent serum, need for hospitalization. Other exclusions - females who are pregnant or breastfeeding or unable to use effective contraception during study period; active liver disease; moderate to severe renal impairment including dialysis, HIV infection with viral load >400 or on prohibited medications; current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4

Study findings: risk of hospitalization for COVID-19 or death from any cause through day 28 was lower with nirmaltrevir/ritonavir (8/1039 participants [0.8 %]) than with placebo (66/1046 [6.3%]) (difference, -5.62 percentage points; 95% confidence interval, −7.21 to -4.03; P<0.001).

Adverse events (all grades regardless of causality): in the treatment group (≥ 1%) that occurred at a greater frequency (≥ 5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the treatment group and 4% in the placebo group. (FDA Fact Sheet EUA 2021)

APPENDIX 1 – DRUG INTERACTIONS WITH RITONAVIR

The list below includes many common interactions, however please consult with a pharmacist prior to prescribing nirmatrelvir/ritonavir to evaluate for drug interactions.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1–adrenoreceptor antagonist	**Alfuzosin** **Doxazosin** **tamsulosin**	↑ alfuzosin ↑ doxazosin ↑ alfuzosin	Co-administration contraindicated due to potential hypotension
Analgesics	**pethidine** **piroxicam** **propoxyphene**	↑ pethidine ↑ piroxicam ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities
Antianginal	**ranolazine**	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions
Antiarrhythmics	**amiodarone** **dronedarone** **flecainide** **propafenone** **quinidine** **flecainide**	↑ antiarrhythmic	Co-administration contraindicated, If combination must be used, monitor for cardiac arrhythmias
Antiarrhythmics	**bepridil** **lidocaine (systemic)**	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available
Anticancer drugs	**apalutamide**	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance
Anticancer drugs	**abemaciclib** **ceritinib** **dasatinib** **encorafenib** **ibrutinib** **ivosidenib** **neratinib** **nilotinib** **ruxolitinib** **venetoclax** **vinblastine** **vincristine**	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. *For further information, refer to individual product label for anticancer drug.*
Anticoagulants	**warfarin** **rivaroxaban** **apixaban**	↑↓ warfarin ↑ rivaroxaban ↑ apixaban	Closely monitor INR if co-administration with warfarin is necessary. Increased bleeding risk with rivaroxaban. Avoid concomitant use. Reduce apixaban dose by 50%. Avoid in patients who would otherwise receive 2.5 mg twice daily.
Anticonvulsants	**carbamazepine** **phenobarbital** **phenytoin** **fosphenytoin** **lamotrigine**	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin ↓ lamotrigine	Co-administration contraindicated due to potential loss of virologic response and possible resistance
Antidepressants	**bupropion** **trazodone** **mirtazapine**	↓ bupropion and active metabolite hydroxybupropion ↑ trazodone ↑ mirtazapine	Monitor for an adequate clinical response to bupropion. Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. *Refer to trazadone product label for further information.* Monitor for increased mirtazapine effects. Dose reduction may be needed.
Anti-diabetic	**Saxagliptin**	↑ saxagliptin	Limit the saxagliptin dose to 2.5 mg daily

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antifungals	**voriconazole** **ketoconazole** **isavuconazonium sulfate** **itraconazole**	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Avoid concomitant use of voriconazole. *Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.*
Anti-gout	**colchicine**	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Anti-HIV protease inhibitors	**amprenavir** **atazanavir** **darunavir** **fosamprenavir** **indinavir** **nelfinavir** **saquinavir** **tipranavir**	↑ protease Inhibitor	*For further information, refer to the respective protease inhibitors' prescribing information.* Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors
Anti-HIV	**didanosine** **delavirdine** **efavirenz** **maraviroc** **nevirapine** **raltegravir** **zidovudine** **bictegravir/ emtricitabine/ tenofovir**	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	*For further information, refer to the respective anti-HIV drugs prescribing information*
Antimycobacterial	**rifampin**	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered
Antimycobacterial	**bedaquiline** **rifabutin**	↑ bedaquiline ↑ rifabutin	*Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.*
Anti-parkison	**bromocriptine**	↑ bromocriptine	If combined, monitor closely for increased bromocriptine toxicities and consider bromocriptine dose reductions.
Anti-platelet	**Ticagrelor**	↑↓ ticagrelor	Co-administration is contraindicated due to increased risk of dyspnea, bleeding.
Antipsychotics	**lurasidone** **pimozide** **clozapine** **aripiprazole** **haloperidol**	↑ lurasidone ↑ pimozide ↑ clozapine ↑ aripiprazole ↑ haloperidol	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias Aripiprazole reductions are recommended for indications other than major depressive disorder. *Refer to aripiprazole product label for further information.*
Antipsychotics	**quetiapine** **olanzapine**	↑ quetiapine ↓ olanzapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. *Refer to the quetiapine prescribing information for recommendations.* Monitor patients receiving combination for reduced clinical effects of olanzapine.
Anti-spasmodic	**Oxybutynin**	↑ oxybutynin	Monitor for signs of increased oxybutynin effects/toxicity (eg, anticholinergic effects)
Anti-viral	**Letermovir**	↓ letermovir	Co-administration is not recommended due to potential for reduction in letermovir plasma concentrations
Calcium channel blockers	**amlodipine** **diltiazem** **felodipine** **nicardipine** **nifedipine** **nimodipine**	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. *If co-administered, refer to individual product label for calcium channel blocker for further information.*
Cardiac glycosides	**digoxin**	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. *Refer to the digoxin product label for further information.*

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Endothelin receptor Antagonists	**bosentan**	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. *Refer to the bosentan product label for further information.*
Ergot derivatives	**dihydroergotamine** **ergotamine** **methylergonovine**	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system
Hepatitis C direct acting antivirals	**elbasvir/grazoprevir, glecaprevir/pibrentasvir** **ombitasvir/paritaprevir/ritonavir and dasabuvir** **sofosbuvir/velpatasvir/voxilaprevir**	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir. *Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.* *Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information.* Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use
Herbal products	**St. John's Wort (hypericum perforatum)**	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance
HMG-CoA reductase inhibitors	**lovastatin** **simvastatin** **atorvastatin** **rosuvastatin**	↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ rosuvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis Discontinue use of statin at least 12 hours prior to initiation of PAXLOVID and reinitiate within 24 hours of Paxlovid completion.
Hormonal contraceptive	**ethinyl estradiol**	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.
Immuno-suppressants	**cyclosporine** **tacrolimus** **sirolimus** **everolimus**	↑ cyclosporine ↑ tacrolimus ↑ sirolimus ↑ everolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. *If co-administered, refer to individual product label for immunosuppressant for further information.*
Long-acting beta-adrenoceptor agonist	**salmeterol**	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	**fentanyl** **methadone** **hydrocodone** **morphine** **tramadol** **oxycodone**	↑ fentanyl ↑ oxycodone ↑ hydrocodone ↑ morphine ↑↓ tramadol ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when opioids are concomitantly administered with PAXLOVID. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	**sildenafil (Revatio®) when used for pulmonary arterial hypertension**	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope
Sedative/ hypnotics	**triazolam** **oral midazolam** **alprazolam** **clonazepam** **diazepam** **trazodone** **zolpidem**	↑ triazolam ↑ midazolam ↑ alprazolam ↑ clonazepam ↑ trazodone ↑ zolpidem	Reduce alprazolam dose by 50% while taking ritonavir Co-administration can increase risk of sedation, Qtc prolongation. Consider a lower dose of trazodone when used with ritonavir. Monitor for increased zolpidem effects and toxicities

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Sedative/ hypnotics	**midazolam (administered parenterally)**	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. *Refer to the midazolam product label for further information.*
Systemic corticosteroids	**betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone, mometasone prednisone triamcinolone**	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.
Thyroid Products	**Levothyroxine**	↓ levothyroxine	Monitor for signs and symptoms of hypothyroidism in patients taking thyroid products with ritonavir. Additional thyroid levels monitoring may be required

FDA FACT SHEETS

FDA EUA Fact sheet for Paxlovid (nirmatrelvir/ritonavir) for healthcare professionals: https://www.fda.gov/media/155050/download, accessed 12/26/21

FDA EUA fact sheet for Paxlovid (nirmatrelvir/ritonavir) for patients, parents, and caregivers: must be given to patient when prescribin:g https://www.fda.gov/media/155051/download, accessed 12/26/21

FDA EUA fact sheet for molnupiravir for healthcare professionals: https://www.fda.gov/media/155054/download, accessed 12/26/21

FDA EUA fact sheet for molnupiravir for patients and caregivers must be given to patient when prescribing: https://www.fda.gov/media/155055/download, accessed 12/26/21

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FUN FACT: Drug prefixes are where creativity may be employed. The prefix mol- of molnupivavir was chosen to invoke Thor's hammer **Mjölnir** (Singh 2021). Thor is the god of thunder and lightning in Norse mythology, as well as a main character of the Marvel Comics Avengers series.