Beth Israel Lahey Health

Outpatient/ (Inpatient if available)
Oral Antiviral Therapies Molnupiravir (MOV) and PAXLOVID (NIRMATRELVIR WITH RITONAVIR)
Emergency Use Authorizations (EUA) based guidelines **LAST UPDATED: Mar 30, 2022**

The purpose of this guideline is to outline the criteria for use of molnupiravir or Paxlovid (nirmatrelvir with ritonavir) in order to fulfill the regulatory requirements of the EUAs and built upon the specific drug characteristics. This guideline will not cover all potential clinical scenarios and clinical judgement is required for optimal application.

Overview

The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the use of these oral antivirals for the following indication(s):

For an electronic toolkit approach for outpatient therapeutics, review the BILH online resource

Medication	Molnupiravir (Lagevrio)	Paxlovid (nirmatrelvir with ritonavir)
EUA	12/23/21, update 3/22	12/22/21
Indications	*Only in the case that alternative treatment options are not available or appropriate*, for outpatient treatment of mild-moderate CoVID-19 infection in patients at high risk for progressing to severe infection and possible hospitalization*	Outpatient treatment of mild-moderate CoVID-19 infection in patients at high risk for progressing to severe infection and possible hospitalization*

***Risk factors defined on page 3. Inpatient use for "incident" CoVID is being operationalized given the rise of BA.2**

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BILH CRITERIA FOR USE OF ORAL ANTIVIRALS FOR COVID 19

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
Overlying restriction	**Lack of viable therapeutic agent or contraindication to another agent**	Not Applicable
Time from symptoms to drug initiation	No greater than **5 days prior**	

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	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
Confirmation of infection and timeframe	PCR or antigen test confirming SARS-CoV-2 infection from a specimen obtained **no greater than 5 days prior** to the date the medication is prescribed	
Symptoms (Mild to moderate) ≥1	fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath with exertion, loss of taste/smell	
Age limits	≥ 18 years	>12 years weighing more than 40kg
Childbearing potential/pregnancy status	People of childbearing potential must use reliable contraception during treatment and for four days later. If pregnant, there is a risk for teratogenicity that needs to be balanced with a potential benefit for avoiding hospitalization for CoVID-19. **Three other agents for use, Paxlovid, Bebtelovimab and Remdesivir should be prioritized over Molnupiravir.**	No specific warnings relative to pregnancy status or the need for barrier contraception. More details on safety in pregnancy in later section.
HIV 1 status	Molnupiravir will not affect HIV antiretroviral therapy nor induce resistance to any class of antiretrovirals.	Paxlovid may in theory induce protease inhibitor resistance to HIV-1, particularly in patients with uncontrolled infection not on therapy.
Presence of Risk factors for progression to severe infection One or more	a. Age ≥60 years b. High Risk Body-Mass Index (BMI): • 25-30 kg/m2 AND not fully vaccinated with primary 1-2 dose series (no vaccination or series completed less than 2 weeks prior) • >30 kg/m2 regardless of vaccination status c. Chronic kidney disease d. Diabetes e. Pregnancy or within 6 months post delivery f. Immunosuppressive conditions (at least one): Autoimmune disease requiring ongoing systemic therapy HIV with any CD4 count Asplenia or functional asplenia Malignancy or primary immunodeficiency as defined on page 3 Taking Immunosuppressive medications as defined on page 3 g. Cardiovascular disease or hypertension h. Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension) i. Sickle cell disease or other hemoglobinopathy j. Neurodevelopmental disorders (for example, cerebral palsy), genetic/metabolic syndromes k. Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19))	

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
	Race/ethnicity that is associated with a higher risk of hospitalization or death from COVID-19, including Black or African American, Hispanic or Latinx, American Indian or Alaska Native	

Moderate-Severely Immunocompromising Health Conditions
Active treatment for solid tumor and hematologic malignancies Defined as any of the following: • Last treatment within 3 months • Remission of malignancy has not been achieved • Receipt of an immunotherapy such as a checkpoint inhibitor within the last year
Receipt of solid organ transplant and taking immunosuppressive therapy
Receipt of CAR-T cell or hematopoietic stem cell transplant (within 2 years of transplant or taking immunosuppressive therapy)
Moderate or severe primary immunodeficiencies (e.g. DiGeorge syndrome, Wiskott-Aldrich, Common Variable Immunodeficiency or hypogammaglobulinemia requiring immunoglobulin therapy)
Advanced (CD4<200 or presence of AIDS-defining illness) or untreated HIV infection
Active systemic treatment with any of the following immunosuppressive medications: • Chronic daily corticosteroid use (>10mg prednisone or equivalent daily) • Alkylating agents (e.g., cyclophosphamide) • Antimetabolites (e.g., azathioprine, methotrexate) • Transplant-related immunosuppressive drugs (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate) • Cancer chemotherapeutic agents classified as severely immunosuppressive • Tumor-necrosis (TNF) blockers (e.g. etanercept, adalimumab, infliximab) • B-cell depleting agents (e.g. rituximab) • Other biologic agents or small molecule inhibitors that are immunosuppressive or immunomodulatory (e.g., IL-1 antagonist, PD-L1, VEGF, EGFR, IL-6, JAK kinase inhibitor)
End-stage renal disease necessitating hemodialysis
Asplenia or functional asplenia

Exclusion Criteria:

- Oxygen saturation (SpO2) ≤ 93% on room air due to COVID-19 in those not on chronic oxygen therapy
- An increase in baseline oxygen flow rate due to COVID-19 in those who are on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
- Respiratory rate ≥ 30 per minute or Heart rate ≥ 125 per minute
- Allergies to molnupiravir or Paxlovid (nirmatrelvir with ritonavir) or any excipients in the preparation
- Co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
- HIV 1 infection and not on combination antiretrovirals

Pharmacology

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Metabolism/ Activation	Metabolized to the cytidine nucleoside analogue, N4-hydroxycytidine (NHC), which distributes into cells where phosphorylation to the active ribonucleoside triphosphate (NHC-TP) occurs.	Nirmatrelvir is the active drug metabolized by the cytochrome 3A4 system to inactive drug. Ritonavir serves to partially inhibit this metabolism extending the half life and exposure to nirmatrelvir. Significant hepatic disease, other drug inhibitors or inducers will affect this metabolism as detailed under drug drug interactions.
Mechanism of action	Active metabolite (NHC-TP) works via viral error catastrophe, also referred to as viral lethal mutagenesis. NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into viral RNA by the viral RNA-dependent RNA polymerase (RdRp, nsp12), results in an accumulation of errors in the viral genome leading to inhibition of replication.	**Nirmatrelvir**: 3CLpro or nsp5 protease inhibitor active against SARS COV2 **Ritonavir:** HIV 1 protease inhibitor and cytochrome P450 enzyme inhibitor (booster of nirmatrelvir)

Dosing and Route of Administration

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Route	Oral only	Oral only
Dose	800 mg (four x 200 mg capsules) q12h	Nirmatrelvir 300 mg (**two** 150 mg tablets) PLUS ritonavir 100 mg tablet BID*
Duration	5 days	5 days
Effects of food	Can be taken with or without food	Take with food to reduce nausea

- See dose adjustments for renal dysfunction

Dose adjustments:

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Renal dysfunction	No dose adjustment required	In patients with **CrCl ≥30 to 59 mL/min**, dose reduce to **150 mg nirmatrelvir** (**one** 150 mg tablet) **PLUS** ritonavir 100 mg tablet BID Not recommended in patients with **estimated CrCl < 30mL/min or requiring dialysis**

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Hepatic dysfunction	No dose adjustment required	Not recommended in patients with Child Pugh C class hepatic dysfunction

Significant Drug- Interactions

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Cytochrome P450 inhibitors	None	Certain drugs are potent inhibitors of the metabolic enzymes for nirmatrelvir resulting in a potential increase in nirmatrelvir levels leading to increased toxicity. Avoid coadministration with voriconazole, posaconazole, cobicistat or drugs coformulated with ritonavir.
Cytochrome P450 substrates	None	A number of drugs are metabolized by the enzyme system inhibited by ritonavir and when used together could result in a potential increase in levels of these drugs leading to increased toxicity. The following drugs are specifically contraindicated to be coadministered given the inability to safely reduce their dose. Other agents may be selected as a substitute with some caveats.
Cytochrome P450 inducers	None	Certain drugs are potent inducers of the metabolic enzymes for nirmatrelvir resulting in a potential decrease in levels leading to potential for loss of virologic response and possible resistance. Avoid coadministration with rifampin, carbamazepine, phenobarbital, phenytoin

Antianginal:	ranolazine
Antiarrhythmics:	amiodarone, dronedarone, flecainide, propafenone, quinidine
Anticancer:	neratinib, venetoclax, ibrutinib
Anticoagulants	rivaroxaban
Antifungals	voriconazole
Anti-gout:	colchicine
Antipsychotics:	lurasidone, pimozide, clozapine
Ergot derivatives:	dihydroergotamine, ergotamine, methylergonovine
HCV direct acting antivirals	glecaprevir/pibrentasvir
HMG-CoA reductase inhibitors	lovastatin, simvastatin
PDE5 inhibitor	Sildenafil at doses needed for pulmonary arterial hypertension (PAH)
Multiple other agents in these and other therapeutic classes may require dose adjustment when given concomitantly. A full review of these agents is available within the EUA or in the BILH prescribing guide.	

Potential Adverse reactions

Medication	Molnupiravir (prodrug)	Paxlovid (nirmatrelvir with ritonavir)
Reproduction	Teratogenicity in animals	Not enough data but experience with ritonavir suggests a low risk.
Bone and cartilage	Cartilage and bone growth abnormalities in patients under 18 years of age based on animal data	None known
General	GI side effects: diarrhea and nausea	GI side effects: diarrhea, dysguesia and nausea, myalgias.
Hepatic	None significant	Hepatic enzyme elevations and hyperbilirubinemia have been reported with ritonavir in previous HIV studies.

Under the EUAs, the FDA is requiring health care providers who prescribe any of these products to report all medication errors and serious adverse events considered to be potentially related to any of these agents through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178.

FDA MedWatch forms should be provided to the corresponding drug company as well:

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
Company	Merck	Pfizer
Fax	215-616-5677	1-866-635-8337
Email	dpoc.usa@msd.com	No email, use website www.pfizersafetyreporting.com
Phone	1- 800-672-6372	1-800-438-1985

Unique Requirements for the EUA by Discipline:
Prescribers

Refer to the BILH online resources for oral antivirals for COVID-19 and online referral form

Review the *EUA Fact Sheet for Providers* and the *inclusion/exclusion criteria*

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
EUA Detailed Fact Sheets	Fact Sheet for Health Care Providers	Fact Sheet for Health Care Providers
Frequently Asked Questions (FAQ) for EUA	FAQ on EUA for Molnupiravir	FAQ on EUA for Paxlovid (nirmatrelvir with ritonavir)

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BILH Checklists-Prescribing information	Molnupiravir Checklist to confirm eligibility Molnupiravir information for prescribers	Nirmatrelvir/ritonavir Prescribing summary

Review the EUA Fact Sheet for Patients/Caregivers with the patient or legally authorized representative. An interpreter is recommended to assist if the patient speaks another language.

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
English Language	FDA Patient/Caregiver Fact Sheet	FDA Patient/Caregiver Fact Sheet
Spanish Language	FDA Patient/Caregiver Fact Sheet	FDA Patient/Caregiver Fact Sheet

Pharmacists

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
EUA Detailed Fact Sheets	Fact Sheet for Health Care Providers	Fact Sheet for Health Care Providers
Frequently Asked Questions (FAQ) for EUA	FAQ on EUA for Molnupiravir	FAQ on EUA for Paxlovid (nirmatrelvir with ritonavir)

Dispensing & inventory information
Molnupiravir capsules are supplied as follows: 200 mg molnupiravir Swedish Orange opaque capsules with corporate logo and “82” printed in white ink
40 count bottles

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.
Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side. Each tablet contains 150 mg of nirmatrelvir.
Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.

Storage

Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
room temperature	room temperature

Pregnancy

	Molnupiravir	Paxlovid (nirmatrelvir with ritonavir)
Animal studies	Fetal harm noted when exposed during pregnancy	Reduced fetal weight noted but no significant fetal demise.
Human studies	Data not available: Patients were excluded if pregnant and all were instructed to use a reliable method	There are no available human data on the use of nirmatrelvir during pregnancy. Other protease inhibitors (darunavir and atazanavir), boosted with ritonavir, are among the first-line recommended

	of birth control during therapy and for three months thereafter	treatment for pregnant people living with HIV and no increased risk of congenital abnormalities or adverse maternal or fetal outcomes have been noted. Older protease inhibitors (lopinavir/ritonavir) have been associated with preterm delivery and low birth weight when used as a chronic medication throughout pregnancy for HIV treatment.
Recommendation	Not recommended in persons confirmed to be pregnant unless risk/benefit has been fully evaluated and the patient has been adequately informed.	Use with appropriate caution in pregnancy as data is limited.
Birth control	People of childbearing potential are advised to use a reliable form of birth control during treatment and for **four days** after the last dose.	No specific recommendations for birth control in either men or women of childbearing potential.

Breastfeeding

	Molnupiravir	**Paxlovid (nirmatrelvir with ritonavir)**
Animal studies	The active metabolite NHC was detected in the plasma of nursing offspring from lactating rats. No details of an adverse effect was noted.	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. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir.
Human studies	Data not available: Patients were excluded if breastfeeding	Data not available: Patients were excluded if breastfeeding
Recommendation	Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.	Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Major studies informing the EUA

	Molnupiravir	**Paxlovid (nirmatrelvir with ritonavir)**
Study	MOVe OUT (MK-4482-002) NEJM Dec 2021	EPIC-HR NEJM Feb 2022
Design	Phase 3 RCT vs placebo	Phase 2/3 RCT vs placebo
Population	775 Outpatients COVID + mild-moderate disease at risk of	2,224 Outpatients COVID + mild-moderate disease at risk of advanced disease

	advanced disease	
Primary Endpoint	Combined: hospitalization or all-cause mortality at day 29	Combined: hospitalization or all-cause mortality through day 28
Outcome	6.8% (treatment) vs. 9.7% (placebo) 30% relative risk reduction P<0.001	0.8% (treatment) vs. 6.3% (placebo) 88.9% relative risk reduction P<0.0001

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