**Oral Anti-Viral Therapy for COVID-19**

Two oral antiviral therapies, nirmatrelvir/ritonavir (Paxlovid) and molnupiravir (Lagevrio), were granted emergency use authorization (EUA) for the treatment of mild-to-moderate COVID-19.

- PAXLOVID has not been approved but has been authorized for emergency use by FDA under an EUA, 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 results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death.
- Molnupiravir has not been approved but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

For adults, determining increased risk for progression can be through the MASS-BP score or by EUA definition.

Treatment is only indicated if <u>within 5 days of symptom onset</u>.

Additional Exclusion Criteria:

***Nirmatrelvir/ritonavir (Paxlovid)***

- eGFR < 30 mL/min
- severe hepatic impairment (Child-Pugh Class C)
- non-modifiable drug-drug interactions
- Age <12 years (or weight <40kg in a pediatric patient)

***Molnupiravir***

- Age <18 years
- Pregnancy

**Nirmatrelvir/Ritonavir (Paxlovid)**

Providers are required to make authorized Fact Sheets available to patients, parents, and caregivers through appropriate means, prior to administration of Paxlovid.

A brief overview is below. Please see the Provider Fact Sheet for full information.

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| MOA | SARS-CoV-2 main (Mpro) protease inhibitor + ritonavir (HIV-1 PI and CYP3A inhibitor) |
| Regimen | • eGFR ≥ 60 mL/min: 2 tablets (300 mg) nirmatrelvir + 1 tablet (100 mg) ritonavir BID x 5 days<br>• eGFR 30-59 mL/min: 1 tablet (150 mg) nirmatrelvir + 1 tablet (100 mg ritonavir) BID x 5 days<br>• Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets |
| Major Study Outcomes | EPIC-HR (n=2,246 adults)<br>• 89% reduction in hospitalization or death through day 28 (0.7% vs. 6.5%) within 3 days of symptom onset<br>• 88% reduction in hospitalization or death through day 28 (0.8% vs. 6.3%) within 5 days of symptom onset |
| Adverse Events | Comparable between Paxlovid (23%) and placebo (24%), most of which were mild in intensity.<br>• dysgeusia (6% vs <1%), diarrhea (3% vs 2%), hypertension (1% vs <1%), and myalgia (1% vs <1%)<br>Serious adverse events potentially related to Paxlovid MUST be submitted to the FDA (form 3500) |
| Contraindications<br><br>AND<br><br>Drug Interactions<br><br>*See Table 1 beginning on page 9 of the Provider Fact Sheet for additional information on specific drug interactions with CYP3A inhibitors and inducers* | • Clinically significant hypersensitivity reactions (TEN or SJS) to any component<br>• Concomitant medications highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:<br>  ○ **Absolute contraindication**: amiodarone, dronedarone, flecainide, propafenone, quinidine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, and sildenafil (when used for PAH)<br>  ○ Contraindicated IF UNABLE TO HOLD while on Paxlovid: alfuzosin, pethidine, piroxicam, propoxyphene, ranolazine, colchicine, lovastatin, simvastatin, triazolam, and oral midazolam.<br>• Concomitant medications that are potent CYP3A inducers. Significantly reduced nirmatrelvir or ritonavir concentrations may be associated with potential for loss of virologic response and possible resistance. Paxlovid cannot be started immediately after discontinuation of any of the following medications due to delayed offset of the recently discontinued inducer: **apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort**<br>• No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat (ritonavir- or cobicistat-containing HIV or HCV regimens should continue treatment as indicated)<br>• Monitor blood pressure while on concomitant calcium channel blockers<br>• Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. *Advise patients to use an additional, non-hormonal (barrier) method of contraception.* |
| Pregnancy & Lactation | No available human data on use of nirmatrelvir in pregnancy (limited animal studies did not show harm). Published observational studies on ritonavir in pregnant women have not identified an increase in major birth defects.<br>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. Limited published data reports that ritonavir is present in human milk (no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production) |

*The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb3(b)(1), unless the declaration is terminated, or authorization revoked sooner.*

**Molnupiravir (Lagevrio)**

Providers are required to provide and document that a copy of the authorized Fact Sheet for Patients and Caregivers has been provided prior to prescribing molnupiravir. They must also inform patients or caregivers of the information detailed in the section *Mandatory Requirements for Administration of Molnupiravir Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

A brief overview is below. Please see the Provider Fact Sheet for full information.

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| MOA | Competitive substrate for virally encoded RNA-dependent RNA polymerase |
| Regimen | • 800mg (4 capsules) by mouth Q12hours x5 days<br>• Advise patients to swallow capsules whole, and to not open, break, or crush the capsules<br>• No renal or hepatic dose adjustments required |
| Major Study Outcomes | MOVe-OUT (n=1,433 adults)<br>Within 5 days of symptom onset (primary outcome):<br>• 30% reduction in hospitalization or death by day 29 (6.8 vs. 9.7%)<br>• Interim analysis more favorable at 7.3% vs. 14.1% which was not replicated in the post-interim analysis population (6.2% vs. 4.7%) |
| Adverse Events | Comparable between molnupiravir (30.4%) and placebo groups (33%). 1-2% of participants reported diarrhea, nausea, or dizziness.<br><br>Serious adverse events potentially related to molnupiravir MUST be submitted to the FDA (form 3500) |
| Contraindications and Warnings | No specific contraindications have been identified based on the limited available data<br><br>**Warnings:**<br>• **Embryo-Fetal Toxicity:** see Pregnancy and Contraception Requirement sections below. Prior to initiating, provider needs to assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.<br>• **Bone and Cartilage Toxicity:** not authorized in patients less than 18 years of age because it may affect bone and cartilage growth based on animal studies<br><br>Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity. |
| Drug Interactions | • No specific drug interactions have been identified based on the limited available data |
| Contraception Requirements | • Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.<br>• Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose. |
| Pregnancy & Lactation | Animal reproduction studies have shown that molnupiravir **may cause fetal harm** when administered to pregnant individuals.<br><br>No data on the presence of molnupiravir or its metabolites in human milk and unknown if an effect on the breastfed infant. However, based on potential for adverse reactions in the infant, breastfeeding is not recommended during treatment and for 4 days after the final dose. |

*The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated, or authorization revoked sooner.*