The Food and Drug Administration (FDA) has granted Emergency Use Authorization (EUA) status for two oral antiviral agents, nirmatrelvir/ritonavir (Paxlovid™) and molnupiravir. Both of these antivirals are the first oral therapies authorized for use in the outpatient setting.

Specific patient criteria under the EUA for the oral antivirals require a patient to have a positive COVID-19 test and symptomatic mild or moderate illness (as defined by NIH):

- **Mild Illness:** Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- **Moderate Illness:** Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥ 94% on room air at sea level.

The current supply allocations may require further prioritization until more adequate supply is received.

Preliminary Phase 3 data suggest nirmatrelvir/ritonavir (Paxlovid™) may be more effective at reducing risk of death and hospitalization, compared to molnupiravir. However, no head-to-head studies are available. Molnupiravir has a narrower indication for use in that it is recommended only when alternatives are not available or clinically appropriate.

Detailed information for each antiviral therapy can be found in the respective EUA FACT SHEETS for HCPs.

- [Nirmatrelvir/ritonavir Fact Sheet for Health Care Providers](#)
- [Molnupiravir Fact Sheet for Health Care Providers](#)

A summary of key clinical comparisons can be found in Table 1 below:

<table>
<thead>
<tr>
<th>Table 1. Clinical Use Comparison</th>
<th>Nirmatrelvir plus Ritonavir (Paxlovid™)</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA issued Emergency Use Authorization (EUA)</td>
<td>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. [Dec. 22, 2021]</td>
<td>For the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults 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, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate. [Dec 23, 2021]</td>
</tr>
</tbody>
</table>
| Exclusions for Use | NOT authorized for use:  
- In patients requiring hospitalization due to severe or critical COVID-19.  
- For pre-exposure or post-exposure Prophylaxis.  
- Duration longer than 5 consecutive days. | NOT authorized for use in:  
- Patients younger than 18 years of age because molnupiravir may affect bone and cartilage growth.  
- Pre-exposure or post-exposure prevention of COVID-19.  
- For initiation of treatment in patients hospitalized due to COVID-19 because benefit of treatment has not been observed in people when treatment started after hospitalization due to COVID-19.  
- Duration longer than 5 consecutive days. |
| Mechanism of Action | • Both nirmatrelvir and ritonavir are protease inhibitors. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) | Viral lethal mutagenesis |
Nirmatrelvir plus Ritonavir (Paxlovid™)

- inhibitor while ritonavir is an HIV protease inhibitor.
- Ritonavir provides boosted activity of nirmatrelvir by inhibiting metabolism (CYP3A inhibitor). It does not have activity against SARS-CoV-2).

### Dosing

**Dosage:** Three tablets: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg RTV (one 100 mg tablet), all taken together twice daily for 5 days.

**Renal Impairment:**
- eGFR ≥ 60: No adjustment needed
- eGFR ≥ 30 to < 60: 150 mg of nirmatrelvir and 100mg RTV twice daily for 5 days
- eGFR <30: not recommended

### Administration

Nirmatrelvir must be co-administered with ritonavir.
- Initiate within 5 days of symptom onset (as soon as possible after diagnosis of COVID-19).
- Administer orally with or without food.

Missed doses – If missed within 8 hours of time usually taken, the patient may take a dose and resume regular schedule.
If the dose missed has been > 8 hours, take the next dose at the regular schedule. Do NOT double the dose.

### Special Populations

**Pregnancy:** No available human data. Observational risk in pregnant women have not identified and increased risk of birth defects or miscarriage.

**Renal Impairment:** Not recommended for use in patients with eGFR < 30 until more data are available.

**Severe Hepatic Impairment (child Hugh Class C):** Not recommended.

### Molnupiravir

Dosage: Four 200 mg (800 mg total) capsules taken orally every 12 hours for five days.

Molnupiravir should be initiated within 5 days of symptom onset (as soon as possible after diagnosis of COVID-19).

Missed doses - If a dose is missed within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule.

If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Do NOT double the dose.

**Pregnancy:** NOT recommended. Animal reproductions studies found that molnupiravir may cause fetal harm when administered during pregnancy. See warnings and precautions for proper birth control. Breastfeeding is also not recommended for at least 4 days after the final treatment dose.

**Renal Impairment:** No dosage adjustments required. The pharmacokinetics has not been studied in patients with an eGFR < 30 or on hemodialysis.

**Hepatic Impairment:** No dosage adjustments required.

### Reported Data Results

<table>
<thead>
<tr>
<th>Efficacy Endpoint – Rate of Reduction (RRR) of hospitalization and death</th>
<th>Nirmatrelvir plus Ritonavir (Paxlovid™)</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment initiated within 3 days of symptom onset: 90% RRR; Treatment initiated within 5 days of symptom onset: 88% RRR.</td>
<td>Treatment initiated within 3 days of symptom onset: 30% RRR when taken within 5 days of symptom onset.</td>
<td></td>
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</tbody>
</table>

**NOTE:** To date, Phase 3 trial for nirmatrelvir/ritonavir unpublished and full critical evaluation unavailable.
**Sutter Health Patient Selection Criteria**

Multiple therapeutic agents are now available for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. These treatments include monoclonal antibody products, remdesivir IV infusion for 3 days, and the oral antiviral agents. Operational limitations, supplies, and patient contraindications determine which treatment might be best. For the latest information, please refer to COVID-19 Treatment Algorithm and COVID-19 Ambulatory Management Algorithm and Guidelines.

Nirmatrelvir/ritonavir and molnupiravir have very different safety profiles and must be considered when selecting best treatment for a patient.

- **Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid™), clinicians should carefully review concomitant medications, including over-the-counter medicines and herbal supplements, to evaluate the potential for drug-drug interactions.**

**MEDICATION SAFETY COMPARISON**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Nirmatrelvir plus Ritonavir</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components.</td>
<td>No contraindications provided by the manufacturer.</td>
<td></td>
</tr>
<tr>
<td>• <strong>Co-administration with drugs highly dependent on CYP3A</strong> for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.</td>
<td></td>
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</tr>
<tr>
<td>• <strong>Co-administration with potent CYP3A inducers</strong> where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Warnings &amp; Precautions</th>
<th>Nirmatrelvir plus Ritonavir</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potentially significant drug interactions (see section below).</td>
<td>Females of child-bearing age should use reliable contraception during treatment and continue for four more days after final dose. Males are advised to use reliable method of birth control during treatment and for at least 3 months after final molnupiravir dose.</td>
<td></td>
</tr>
<tr>
<td>• Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.</td>
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<td></td>
</tr>
<tr>
<td>• HIV-1 Drug Resistance: use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.</td>
<td>Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Selected Drug Interactions</th>
<th>Nirmatrelvir plus Ritonavir</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>A comprehensive list of established and other potentially significant drug-drug interactions can be found in Table 1 within the Paxlovid Emergency Use Full Prescribing Info HCP Fact Sheet.</td>
<td>No drug interactions have yet been identified.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Nirmatrelvir plus Ritonavir</th>
<th>Molnupiravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (incidence ≥1% and ≥5 subject difference): dysgeusia, diarrhea, hypertension, and myalgia.</td>
<td>Diarrhea, nausea, and dizziness were the most frequent occurring side effects. The incidence (1-2%) was equal to that seen in the placebo treated group.</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Event Reporting**

As part of the EUA, health care providers will be required to report to FDA MedWatch, using FDA Form 3500, all medication errors and serious adverse events potentially associated with Paxlovid™ or molnupiravir within 7 calendar days from event onset. Reports can be submitted online via [http://www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

Prepared by System Pharmacy/FMCP 12-30-2021