OUTPATIENT GUIDANCE FOR TREATMENT
OF COVID-19 IN ADULTS AND CHILDREN

These are interim treatment recommendations based on best available evidence at this time. Recommendations may be modified based on resource availability, testing recommendations, and future published data.

Clinical symptoms range from uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

Testing:
See link to current COVID-19 testing recommendations: Send testing for COVID-19

Prevention:
See link to institutional Evusheld (tixagevimab-cilgavimab) criteria

Treatment:

<table>
<thead>
<tr>
<th>Supportive Care</th>
<th>Monoclonal Antibody</th>
<th>Oral Antiviral</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Paxlovid)</td>
<td>(Molnupiravir)</td>
<td></td>
</tr>
</tbody>
</table>

Please see detailed prescribing recommendations in the COVID outpatient treatment guidelines and the State eligibility criteria for Paxlovid and molnupiravir

Further, please factor symptom duration and relevant drug-drug interactions with Paxlovid into treatment decisions.

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>remdesivir x 3 days (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age ≥12, ≥40 kg</td>
<td>age ≥18</td>
<td>age ≥28 days, ≥3 kg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom onset range (to start therapy within)</th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>remdesivir x 3 days (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sx ≤5 days¹</td>
<td>Sx ≤5 days¹</td>
<td>Sx ≤7 days¹</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>Oral Antiviral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate COVID in a patient at high risk for progression to severe COVID-19²</td>
<td>Alternative to consider ONLY if patient cannot get Paxlovid nor mAb</td>
<td>Regardless of vaccination status with one of the following: • Absolute drug contraindication to Paxlovid AND severe³ or moderate⁴ immunocompromise</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>Oral Antiviral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate for DDI</td>
<td>Not for use in pregnancy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: For patients with solid organ transplant, paxlovid should be used (with monitoring) unless they are on envarsus or mTOR inhibitors, or are on other medications that are an absolute contraindication to paxlovid (ie amiodorone)

¹First day of symptoms counts as day 0 (i.e., if symptoms started on Monday (day 0), Saturday would be day 5)
²CDC risk factors include (not all inclusive): Age ≥65 years, immunosuppression, chronic lung disease, chronic kidney disease, chronic liver disease, neurological conditions, diabetes, down syndrome, heart conditions, mental health conditions, BMI ≥25, sickle cell disease or thalassemia, smoking, cerebrovascular disease, substance use disorders, tuberculosis
³Severe immunocompromise: solid organ transplant, bone marrow transplant, hematologic malignancy, on b-cell depleting therapy (i.e., on rituximab)
⁴Moderate immunocompromise: Primary immunodeficiency, active malignancy and receiving chemotherapy, autoimmune diseases requiring immunosuppressive therapy (hydroxychloroquine or sulfasalazine alone is not sufficient), advanced or untreated HIV infection
⁵Up-to-date w/vaccines = a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible

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¹See comments below regarding evaluation of risk in present day.
Paxlovid is the preferred therapeutic agent if the patient can obtain and start the medication in a timely manner (≤5 days of symptom onset). Remdesivir for 3 days is an appropriate alternative for those who are immunocompromised and cannot receive Paxlovid (due to drug drug interactions, timing of symptoms, or contraindications). Molnupiravir is inferior to both Paxlovid and remdesivir, and should only be considered for use if both Paxlovid and remdesivir therapy are unavailable.

EPIC-HR, the clinical trial supporting FDA emergency use authorization for Paxlovid, enrolled immune-naïve patients (unvaccinated and without prior confirmed COVID-19) with additional characteristics or conditions placing them at a high risk of hospitalization or death (such as advanced age or significant comorbidities). This study, conducted when the Delta variant was dominant, demonstrated an 88% relative risk reduction in hospitalization or death (6.3% in placebo group vs. 0.8% in the treatment group). However, the results of this study are not directly applicable to present-day patients, as >90% of the elderly population has received at least a primary vaccination series, the vast majority of the entire population has evidence of immunity from prior infection and/or vaccination, and a different, less virulent, variant (Omicron) predominates. EPIC-SR, a clinical trial including high-risk vaccinated patients also conducted during the Delta wave, failed to demonstrate a significant benefit with Paxlovid in either time to symptom resolution or in progression to hospitalization or death. One reason for this lack of benefit in the prevention of hospitalization was the very low (<2%) hospitalization rate in untreated patients in this trial, making statistical significance hard to achieve in a registry trial of ~1,000 patients. In a much larger observational study conducted during the Omicron time period in patients with some evidence of prior immunity (vaccination, infection, or both, the hospitalization rate in high-risk, untreated patients was 0.5% in patients age 40-64 and 1.9% in those age ≥ 65. In this study, receipt of Paxlovid was only associated with a decreased risk of hospitalization only in those age ≥ 65. However, given the low hospitalization rate in untreated patients aged 40-64, it would be difficult to demonstrate a significant decrease with Paxlovid use in a observational study. As a result, the likely number needed to treat to prevent one hospitalization with Paxlovid changes from ~15 (unvaccinated, high risk), to ~100 (vaccinated patients ≥ 65 years of age), to substantially higher in the Omicron period in patients under 65 years of age. In contrast, there are potential risks to treatment with Paxlovid that must be considered, including many drug-drug interactions (with different levels of complexity/importance) and a high rate of dysgeusia (up to 50% in real world assessments).

Present day patients at the highest risk include those with older age, a decreased likelihood of an adequate immune response to vaccination (immunocompromising condition/medications), a prolonged time since last vaccination (not up-to-date), and those with multiple risk factors. For example, a 64-year-old overweight patient with congestive heart failure and diabetes would be at higher risk than a 40-year-old with hypertension that recently received their bivalent booster. Therefore, although the EUA allows for the full list of CDC risk factors to qualify a patient for treatment, the antimicrobial stewardship program agrees with the NIH guidelines, which recommend that clinicians use their discretion in assessing an individual patient’s risk for progression to severe disease.

Key Take Away Points:

- Vaccination, and/or prior infection, continues to provide excellent protection from hospitalization and/or death
- Omicron, the current dominant variant, is less virulent
- Taken together, patients at lower risk for progression to severe disease have very low event rates (hospitalization or death), so Paxlovid is less likely to provide a benefit
- Present day patients at the highest risk include those with older age, a decreased likelihood of an adequate immune response to vaccination (immunocompromising condition/medications), a prolonged time since last vaccination (not up-to-date), and those with multiple risk factors.
- It is reasonable, when discussing Paxlovid with patients at lower risk, to use shared decision making, and discuss that there may be very little benefit from this medication compared to potential harms, and it is not strongly recommended for them.
1. Supportive care:

*Supportive care is the mainstay of treatment for non-hospitalized patients.*

2. Remdesivir 3 day infusion:

A clinician must place a “Referral for COVID 3 day Remdesivir Treatment” order, which will go directly to the COVID mAb/RDV trained pharmacy team. If a patient is potentially eligible and capacity allows, the patient will be contacted to discuss symptom duration and consent and proceed with scheduling the infusion based on capacity available. Due to the limited supply, not all patients referred will be able to be treated.

Patients will receive the medication IV as 30 minute infusion, followed by fifteen minutes of observation afterwards. Rarely, patients could experience an allergic reaction or an infusion-related reaction during the infusion.

### Table 1. Michigan Medicine 3 day Remdesivir Eligibility Criteria

<table>
<thead>
<tr>
<th>Priority group: Patients who have severe immunocompromise(^1) with an absolute drug contraindication to paxlovid will be prioritized. Patients with mild or moderate COVID-19 who meet criteria #1-4</th>
</tr>
</thead>
</table>
| 1. Outpatient  
2. No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)  
3. Symptoms ≤7 days  
4. Age ≥28 days and ≥3 kg (regardless of vaccination status) AND an absolute drug contraindication to Paxlovid\(^2\) one of the following:  
   a) Severe\(^1\) immunocompromise  
   b) Moderate\(^2\) immunocompromise |

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\(^1\)Severe immunocompromise: solid organ transplant, bone marrow transplant, hematologic malignancy, on b-cell depleting therapy (i.e., on rituximab)  
\(^2\)For patients with solid organ transplant, paxlovid should be used (with monitoring) unless they are on envarsus or mTOR inhibitors, or are on other medications that are an absolute contraindication to paxlovid (i.e amiodorone)  
\(^3\)Moderate immunocompromise: Primary immunodeficiency, active malignancy and receiving chemotherapy, autoimmune diseases requiring immunosuppressive therapy (hydroxychloroquine or sulfasalazine alone is not sufficient), advanced or untreated HIV infection
3. Oral antivirals
The FDA issued Emergency Use Authorization (EUA) for two novel antiviral agents, ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir, for the treatment of non-hospitalized adults with mild-to-moderate COVID-19 who are at high risk of progression to severe disease. Key information regarding these therapies is provided below; the full FDA Fact Sheets (molnupiravir) (ritonavir-boosted nirmatrelvir) should be referred to for more details. Paxlovid is now widely available at pharmacies throughout the State of Michigan, and prescribing does not need to be restricted to Meijer. MM pharmacy will not be receiving supply.

**Paxlovid (nirmatreliver tablet and ritonavir tablets), manufactured by Pfizer, for COVID-19 treatment**

<table>
<thead>
<tr>
<th>Table 2. State of Michigan Eligibility Criteria for Paxlovid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with mild or moderate COVID-19 who meet criteria #1-9</td>
</tr>
<tr>
<td>1. Age ≥12 years and ≥40 kg</td>
</tr>
<tr>
<td>2. Outpatient</td>
</tr>
<tr>
<td>3. No requirement for supplemental oxygen (no increase from baseline supplemental oxygen)</td>
</tr>
<tr>
<td>4. Symptoms ≤5 days</td>
</tr>
<tr>
<td>5. Not received bebtelovimab or molnupiravir</td>
</tr>
<tr>
<td>6. EGFR ≥30 mL/min (see section on Paxlovid dosing)</td>
</tr>
<tr>
<td>7. Not have severe liver disease (Child-Pugh Class C)</td>
</tr>
<tr>
<td>8. No drug-drug interaction that are absolute contraindications (see Paxlovid Drug-Drug Interaction Summary)</td>
</tr>
<tr>
<td>9. At high risk for progression to severe disease (including pregnancy)</td>
</tr>
</tbody>
</table>

1 CDC risk factors include (not all inclusive): Age ≥65 years, immunosuppression, chronic lung disease, chronic kidney disease, chronic liver disease, neurological conditions, diabetes, down syndrome, heart conditions, mental health conditions, BMI ≥25, sickle cell disease or thalassemia, smoking, cerebrovascular disease, substance use disorders, tuberculosis, pregnancy.

For pregnant patients, a risk-benefit discussion should occur between provider and patient based on individual risk factors. For example, Paxlovid may not provide significant benefit in a patient with a low risk of developing severe disease, such as a pregnant patient without other risk factors for severe disease and up-to-date on vaccination. However, Paxlovid should not be withheld if the patient desires treatment and there are no absolute contraindications (e.g. medication interactions, GFR <30). From a safety standpoint, per guidance from the NIH, "ritonavir has been used extensively during pregnancy in people with HIV and has a documented safety profile during pregnancy. The mechanisms of action for both nirmatrelvir and ritonavir and the results of animal studies of ritonavir-boosted nirmatrelvir suggest that this regimen can be used safely in pregnant individuals. Ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment. The risk-benefit assessment for using ritonavir-boosted nirmatrelvir in pregnant patients may include factors such as medical comorbidities, body mass index, and vaccination status. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent." (NIH COVID treatment guidelines)

**Paxlovid Dosing**
- Standard dose is nirmatrelvir 300 mg (two 150 mg tablets) and ritonavir 100 mg (one 100 mg tablet) orally, with all three tablets taken together, twice daily for 5 days.
- eGFR 30-59 mL/min, the dose is 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.
- Paxlovid is not recommended for patients with severe renal impairment (eGFR <30 mL/min) or severe hepatic impairment (Child-Pugh Class C).

**Paxlovid Drug Interaction Information**
- Prior to starting a patient on Paxlovid, clinicians must carefully review concomitant medications, including over the counter and herbal products.
- If absolute contraindications, then refer for monoclonal antibody therapy.
- Paxlovid has significant drug-drug interactions (DDIs).
  - Nirmatrelvir is a substrate of CYP3A, so concomitant administration of strong inducers (i.e., rifampin) may lead to substantial decreases in Paxlovid concentrations, potentially reducing effectiveness.
  - Nirmatrelvir is co-formulated with ritonavir. Ritonavir is a strong CYP3A4 inhibitor and is used to increase the exposure of nirmatrelvir to effective concentrations but also inhibits the metabolism of many other drugs, potentially leading to toxicities.
- See Paxlovid Drug-Drug Interaction Summary for general management of interacting medications as well as directions for seeking pharmacist consultation.
- The Paxlovid Fact Sheet and the Liverpool COVID-19 Drug Interactions website are also resources to identify and manage DDIs.
Paxlovid Ordering Process

- The following smartphrases can be used to aid in triaging patient symptoms and treatment decision making:
  - .AMBSPECIALTYCOVIDTXSCREENING is ready to be used by any staff to collect information from a patient that will help the provider decide on appropriateness and selection of therapy.
  - .AMBCOVIDTXSCREENING is also for staff to collect information, but this is being used specifically for primary care workflows.
  - .AMBCOVIDTXPROVIDER is for all providers to use to help walk them through decisions regarding treatment. It links to the Drug-Drug interaction links, and then records thought-process and discussion in the note.
- Review the following with the patient:
  - Potential adverse events (dysgeusia, diarrhea, myalgia, hypertension, hepatic injury) and pertinent drug interactions.
  - FDA has authorized emergency use of Paxlovid but Paxlovid is not FDA approved
- Provide electronically the FDA Fact Sheet for Patients/Caregivers via email or patient portal
  - MDHHS Prescription Template can be faxed in the event the ePrescribing is unavailable
- Prescribe Paxlovid and in “Patient sig” section after “Patient criteria:”, type in the free text box the specific state eligibility criteria met by the patient AND date of symptom onset
  - Not including eligibility criteria can lead to rejection of prescription
  - Though GFR is not required, some pharmacists have been rejected scripts without GFR, despite education from MDHHS against this. Given that, GFR if in the last 3 years is automatically put into the script, or is a wildcard to add in case of external lab. If you do not have a reason to be concerned about the patient’s renal function, even if they don’t have a recent GFR, you are not required to have a BMP drawn, and can use your clinical judgement.
- Advise patients to fill the script and start taking the medication as soon as possible.
- During pharmacy business hours, prescriptions should be ready for pick up within 30 minutes. Patient should avoid entering the store for prescription pick up. Advise patient that:
  - Medication should be picked up and started as soon as possible and must be picked up within 5 days of symptom onset.
  - The medication is provided at no cost. The pharmacy may request insurance information, if available, for dispensing costs. There should not be out of pocket charges to patient.
  - Patients should use the drive-through window to pick-up prescription.
  - If patient has barriers to transportation that would delay picking up the medication, free home delivery may be arranged at Meijer pharmacies by having patient contact the pharmacy. Delivery will be made a priority but will likely result in a delay over pharmacy pick-up.

Molnupiravir ( Manufactured by Merck)

• The FDA has granted an Emergency Use Authorization (EUA) of this drug for use in adults 18 years and older with mild-moderate COVID-19 within the first 5 days of symptoms and are at high risk of progression to severe COVID-19 disease, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

• A large, open-label randomized controlled trial (PANORAMIC) of over 25,000 patients randomized to molnupiravir vs supportive care did not demonstrate an association of molnupiravir at preventing hospitalization or death. This was completed in a population with high rates of prior vaccination and/or infection, in the era of (less virulent) Omicron as the dominant variant. It did show a decrease in time to symptom relief of 4 days, though this is less reliable in an open label trial. Additionally, a reduction in time to symptom relief was not seen in the MoVE-OUT trial (blinded RCT), calling this finding further into question. At this time, molnupiravir is still available through the FDA EUA, but it is unlikely to decrease risk of progression to severe disease.

Table 3. State of Michigan Eligibility Criteria for Molnupiravir

<table>
<thead>
<tr>
<th>Patients with mild or moderate COVID-19 who meet criteria #1-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adults ≥18 years</td>
</tr>
<tr>
<td>2. No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)</td>
</tr>
<tr>
<td>3. Symptoms ≤5 days</td>
</tr>
<tr>
<td>4. Cannot receive bebtelovimab or Paxlovid</td>
</tr>
<tr>
<td>5. Not pregnant</td>
</tr>
<tr>
<td>6. At high risk for progression to severe disease1</td>
</tr>
</tbody>
</table>

1CDC risk factors include (not all inclusive): Age ≥65 years, immunosuppression, chronic lung disease, chronic kidney disease, chronic liver disease, neurological conditions, diabetes, down syndrome, heart conditions, mental health conditions, BMI ≥25, sickle cell disease or thalassemia, smoking, cerebrovascular disease, substance use disorders, tuberculosis

Dosing of Molnupiravir

• Standard dose of molnupiravir: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. There are no adjustments for renal and/or hepatic impairment

Drug Interactions

• No significant drug interactions

Molnupiravir Ordering Process

• Review the following with the patient:
  o Potential adverse events
  o Breast feeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. Patient may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir
  o Not to be used in pregnancy. Advise that patients who are pregnant due to potential fetal-embryo toxicity. Women of child-bearing age should do a pregnancy test if there is concern for pregnancy.
  o 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.
  o 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
  o FDA has authorized emergency use of molnupiravir but it is not FDA approved

• Provide electronically the FDA Fact Sheet for Patients/Caregivers via email or patient portal
  o MDHHS Prescription Template can be faxed in the event the ePrescribing is unavailable

• Prescribe molnupiravir and in "Patient sig" section after "Patient criteria:", type in the free text box the specific state eligibility criteria met by the patient AND date of symptom onset
  o Not including eligibility criteria can lead to rejection of prescription

• During pharmacy business hours, prescriptions should be ready for pick up within 30 minutes. Patient should avoid entering the store for prescription pick up. Advise patient that:
- Medication should be picked up and started as soon as possible and must be picked up within 5 days of symptom onset.
- The medication is provided at no cost. The pharmacy may request insurance information, if available, for dispensing costs. There should not be out of pocket charges to patient.
- Patients should use the drive-through window to pick-up prescription.
- If patient has barriers to transportation that would delay picking up the medication, free home delivery by Meijer pharmacies may be arranged by having patient contact the pharmacy. Delivery will be made a priority but will likely result in a delay over pharmacy pick-up.
As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

If obtained from a source other than med.umich.edu/asp, please visit the webpage for the most up-to-date document.
Antimicrobial Subcommittee Approval: N/A
P&T Approval: N/A

Revision History:
12/2/20: Added mAb EUA information
12/11/20: Added information on common side effects of mAb therapy
1/8/21: Added mAb eligibility criteria
1/13/21: Added cardiovascular disease criteria
3/15/21: Added bamlanivimab + etesevimab information
4/7/21: Removed bamlanivimab monotherapy reference, adjusted eligibility criteria
6/7/21: Revised mAb criteria and casirivimab + imdevimab hyperlinks
8/10/21: Revised mAb selection and added post-exposure prophylaxis hyperlink.
9/7/21: Revised mAb criteria
10/14/21: Added inhaled corticosteroid section and added sotrovimab
11/12/21: Revised mAb criteria
12/24/21: Removed bamlanivimab + etesevimab & casirivimab + imdevimab, added oral antiviral information
1/3/22: Revised oral antiviral information
1/10/22: Added Evusheld hyperlink, revised mAb criteria, revised Paxlovid DDI section, added flowchart
1/17/22: Revised Paxlovid and molnupiravir criteria
1/18/22: Revised up-to-date w/vaccines criteria
1/19/22: Revised Paxlovid criteria
1/20/22: Revised molnupiravir criteria
1/24/22: Revised mAb criteria
1/28/22: Revised Paxlovid and molnupiravir criteria, added screening smartphrases
2/4/22: Revised criteria, removed algorithm
2/17/22: Revised mAb information and mAb criteria
2/25/22: Revised Paxlovid and molnupiravir criteria
3/4/22: Revised mAb criteria
7/14/22: Removed inhaled corticosteroid section
8/25/22: Revised pregnancy mAb criteria
10/31/22: Removed mAb therapy, adjusted remdesivir criteria

The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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