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 (Paxlovid) (Molnupiravir)</th>
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<tbody>
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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></th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>bebtelovimab (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographics</td>
<td>age ≥12, ≥40 kg</td>
<td>age ≥18</td>
<td>age ≥12, ≥40 kg</td>
</tr>
<tr>
<td>Symptom onset range (to start therapy within)</td>
<td>Sx ≤5 days¹</td>
<td>Sx ≤5 days¹</td>
<td>Sx ≤7 days¹</td>
</tr>
<tr>
<td>Relative risk reduction in hospitalization or death</td>
<td>88%</td>
<td>30%</td>
<td>85%</td>
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<tr>
<td>Criteria</td>
<td>Mild-moderate COVID in a patient at high risk for progression to severe COVID-19²</td>
<td>Alternative ONLY if patient cannot get Paxlovid nor mAb</td>
<td>Regardless of vaccination status with one of the following: • Severe⁴ immunocompromise • Absolute drug contraindication to Paxlovid AND moderate⁴ immunocompromise Not up-to-date⁵ on vaccines with one of the following: • Absolute drug contraindication to Paxlovid AND additional CDC risk factor for severe disease (including pregnancy)³</td>
</tr>
<tr>
<td>Notes</td>
<td>Evaluate for DDI</td>
<td>Not for use in pregnancy</td>
<td>Preferred in severe immunocompromise⁴</td>
</tr>
</tbody>
</table>

¹ First day of symptoms counts as day 0 (i.e., if symptoms started on Monday (day 0), Saturday would be day 5)
² 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
³ Severe immunocompromise: solid organ transplant, bone marrow transplant, hematologic malignancy, on b-cell depleting therapy (i.e., on rituximab)
⁴ 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
⁵ Up-to-date w/vaccines = a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible (5 months after primary series)
Paxlovid and monoclonal antibody therapy are equally efficacious (88% vs. 85% risk reduction of hospitalization or death due to COVID-19). Paxlovid is the preferred therapeutic agent if the patient can obtain and start the medication in a timely manner (≤5 days of symptom onset), unless the patient is severely immunocompromised or pregnant. Monoclonal antibody is an appropriate alternative for those who cannot receive Paxlovid (due to drug availability, timing of symptoms, or contraindications). Molnupiravir is inferior to both Paxlovid and monoclonal antibody (30% risk reduction) and should only be used if both Paxlovid and monoclonal antibody therapy are unavailable.

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

2. Monoclonal antibody infusion: 
   
   The FDA has issued an EUA for bebtelovimab for non-hospitalized adults and adolescents (12-17 years old) with mild to moderate symptoms (not requiring oxygen supplementation) of COVID-19 with risk factors for progression to severe disease (see Michigan Medicine Eligibility Criteria). Monoclonal antibody therapy for COVID have been developed to bind to the spike protein of SARS-CoV-2 and block the virus from invading human cells. Research suggests that it may reduce the chances that high-risk patients with mild to moderate COVID-19 will develop severe disease that requires a visit to the emergency department and/or hospitalization.

   The goal is to give the medication as early in the course of disease as possible. The criteria utilized to identify patients with risk factors for severe disease have been approved by the Scarce Resource Allocation Committee and will be re-evaluated based on drug supply and infusion capacity.

   **A clinician must place a “Referral for COVID-19 Monoclonal Antibody Treatment” order, which will go directly to the COVID mAb 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 can also be referred to the MDHHS COVID Therapeutics webpage to seek out other sites for possible treatment.

   Patients will receive the medication IV as 30 second to 30-minute infusion, depending on product available. One hour of observation afterwards is required. Rarely, patients could experience an allergic reaction or an infusion-related reaction during the infusion (~1% in the COMET-ICE study).

<table>
<thead>
<tr>
<th>Table 1. Michigan Medicine Monoclonal Antibody Eligibility Criteria</th>
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<tbody>
<tr>
<td>A patient must have had a Michigan Medicine encounter in the last 5 years <strong>OR</strong> be a Michigan Medicine employee <strong>OR</strong> be a University of Michigan student <strong>OR</strong> be a resident of Washtenaw County</td>
</tr>
</tbody>
</table>

**Priority group:** Patients who are pregnant, have severe immunocompromise³, and/or have absolute drug contraindications will be prioritized. Other patients in this group should be prescribed Paxlovid if it is available.

Patients with mild or moderate COVID-19 who meet criteria #1-4 **AND** either criteria #5 **OR** criteria #6:

1. **Outpatient**
2. **No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)**
3. **Symptoms ≤7 days**
4. **Not received Paxlovid**
5. **Age ≥12 years and ≥40 kg (regardless of vaccination status) AND one of the following:**
   a) **Severe immunocompromise³**
   b) **Moderate⁴ immunocompromise AND an absolute drug contraindication to Paxlovid**
6. **Not up-to-date w/vaccines⁵ AND one of the following:**
   a) **CDC risk factor for severe disease (including pregnancy)² AND absolute drug contraindication to Paxlovid**

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 (5 months after primary series)
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 (nirmatrelvir tablet and ritonavir tablets), manufactured by Pfizer, for COVID-19 treatment

Table 2. State of Michigan Eligibility Criteria for Paxlovid

<table>
<thead>
<tr>
<th>Patients with mild or moderate COVID-19 who meet criteria #1-9</th>
</tr>
</thead>
<tbody>
<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 (or 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>
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<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>

 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:
  o .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.
  o .AMBCOVIDTXSCREENING is also for staff to collect information, but this is being used specifically for primary care workflows.
  o .AMBCOVIDTXPROVIDER is for all providers to use to help walk them through decisions regarding treatment. It includes links to the Drug-Drug interaction links, and then records thought-process and discussion in the note.
• Review the following with the patient:
  o Potential adverse events (dysgeusia, diarrhea, myalgia, hypertension, hepatic injury) and pertinent drug interactions.
  o 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
  o 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
  o Not including eligibility criteria can lead to rejection of prescription
• Advise patients to fill the script and start taking the medication as soon as possible. Paxlovid has similar efficacy to monoclonal antibody in trials. Patients not in the priority group for mAb cannot request mAb over Paxlovid if Paxlovid is available.
• 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:
  o Medication should be picked up and started as soon as possible and must be picked up within 5 days of symptom onset.
  o 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.
  o Patients should use the drive-through window to pick-up prescription.
  o 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.

- At this time, given capacity and supply limitations for monoclonal antibody, all patients not eligible for mAb or Paxlovid should be prescribed molnupiravir if desired.

- **In high-risk Tier 1A patients with an absolute drug contraindication to Paxlovid, if infusion slot or drug availability of bebtelovimab cannot be confirmed by day 5 of symptoms, molnupiravir can be prescribed (unless contraindicated due to pregnancy), and this will not preclude the patient from getting mAb if supply/treatment slot becomes available by day 7. But, as a reminder, given the scarcity of bebtelovimab and the decreased efficacy of molnupiravir compared to Paxlovid and bebtelovimab, all efforts should be made to prescribe Paxlovid if safe drug adjustments are possible.**

### Table 3. State of Michigan Eligibility Criteria for Molnupiravir

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Adults ≥18 years</td>
</tr>
<tr>
<td>2.</td>
<td>No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)</td>
</tr>
<tr>
<td>3.</td>
<td>Symptoms ≤5 days</td>
</tr>
<tr>
<td>4.</td>
<td>Cannot receive bebtelovimab or Paxlovid</td>
</tr>
<tr>
<td>5.</td>
<td>Not pregnant</td>
</tr>
<tr>
<td>6.</td>
<td>At high risk for progression to severe disease&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>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

### 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:
  - Potential adverse events
  - 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
  - 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.
  - 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.
  - 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
  - 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
  - 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
  - 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:
  o Medication should be picked up and started as soon as possible and must be picked up within 5 days of symptom onset.
  o 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.
  o Patients should use the drive-through window to pick-up prescription.
  o 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.
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.

If obtained from a source other than med.umich.edu/asp, please visit the webpage for the most up-to-date document.