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

Treatment:

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<td>(Paxlovid) (Molnupiravir)</td>
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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.

In summary:

A. **Prescribe Paxlovid AND refer for monoclonal antibody simultaneously:** *They will only be able to get one therapy, but to provide maximum access to therapeutics for high-risk patients, at this time please also concomitantly place a referral for COVID-19 mAb (i.e., do not want to delay review for sotrovimab infusion in patients who cannot obtain Paxlovid because supply ran out at pharmacy).*
   a. Regardless of vaccination status:
      i. Immunocompromised, if drug-drug interactions can be managed or do not exist; (allowed in pregnancy if other criteria, immunocompromised, are met)
   b. Not maximally vaccinated:
      i. Age 75 or older, if drug-drug interactions can be managed or do not exist

B. **Refer for monoclonal antibody only:**
   a. Regardless of vaccination status:
      i. Immunocompromised, with drug-drug interactions that are absolute contraindications to prescribing Paxlovid
   b. Not maximally vaccinated:
      i. Pregnant
      ii. Age 75 or older and with drug-drug interactions that are absolute contraindications to prescribing Paxlovid

C. **Prescribe molnupiravir:**
   a. Not maximally vaccinated:
      i. 65-74 years old with an additional risk factor for severe disease
   b. If a patient in group A or B cannot be treated with preferred therapy
      i. For sotrovimab, if supply is not available or treatment slots are filled, the pharmacist will route back to the provider who placed the referral, so they can prescribe molnupiravir if still within the 5-day symptom window.
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 sotrovimab 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). This is a monoclonal antibody that has 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. Primary care physicians will be notified if their patient is contacted to discuss the infusion. Due to the overwhelming demand, not all patients referred will be able to be treated. Patients can also be referred to the [MDHHS COVID Therapeutics webpage](https://www.michigan.gov/coronavirus) to seek out other sites for possible treatment.

   Patients will receive the medication IV as an approximately 30-minute infusion. 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).

   The most common reported symptoms after the infusion are nausea, diarrhea, dizziness, vomiting, myalgias, headache, and malaise. These symptoms did not occur more frequently in patients receiving the monoclonal antibody infusion when compared to the placebo group. Thus, for most patients such symptoms are more likely to be related to COVID-19 rather than the infusion. Patients receiving a monoclonal antibody infusion are also still at risk for progression to severe disease.

   Therefore, a patient complaining of worsening shortness of breath in the few days following the infusion could be experiencing COVID-19 progression OR a delayed reaction to the infusion. Irrespective of the underlying cause, they should be evaluated urgently. Patients without shortness of breath or other concerns requiring emergent evaluation in the ED can be managed with supportive care (i.e., ibuprofen, acetaminophen, fluids, anti-emetics, loperamide).

   **Table 1. Michigan Medicine Monoclonal Antibody Eligibility Criteria**

   A patient must have had a Michigan Medicine encounter in the last 5 years **OR** be a Michigan Medicine employee **OR** be a University of Michigan student **OR** be a resident of Washtenaw County

   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 or molnupiravir
   5. Age 12 or older and ≥40 kg (regardless of vaccination status)
      a) Immunosuppressed
         i) Moderate or Severe Primary immunodeficiency
         ii) SOT of immunosuppressive medications
         iii) Active malignancy and receiving chemotherapy
         iv) Hematopoietic stem cell transplant in last 2 years or receiving immunosuppressive therapy
         v) Autoimmune diseases requiring immunosuppressive therapy
         vi) Advanced or untreated HIV infection
   6. Not maximally vaccinated* **AND**:
      a) Pregnancy
      b) Age ≥75

   * Maximally vaccinated = completion of all recommended vaccines for age group, including booster
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. Currently only Meijer Pharmacies will be receiving supply of both antiviral. MM pharmacy will not be receiving supply.

Paxlovid (nirmatrelvir 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>
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</thead>
<tbody>
<tr>
<td>Patients with mild or moderate COVID-19 who meet criteria #1-8</td>
</tr>
<tr>
<td>1. Adults and adolescents 12 years and older who weigh at least 88 lbs (40 kg)</td>
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<tr>
<td>2. Outpatient</td>
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<tr>
<td>3. No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)</td>
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<tr>
<td>4. Symptoms ≤5 days</td>
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<tr>
<td>5. Not received sotrovimab or molnupiravir</td>
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<tr>
<td>6. EGFR ≥30 mL/min (see section on Paxlovid dosing)</td>
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<tr>
<td>7. No drug-drug interaction that are absolute contraindications (see Table 2)</td>
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<td>8. One of the following:</td>
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<tr>
<td>a) Age ≥75 years AND not maximally vaccinated*</td>
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<tr>
<td>b) Immunosuppressed -regardless of vaccination status:</td>
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<tr>
<td>†. Moderate or Severe Primary immunodeficiency</td>
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<td>‡. SOT on immunosuppressive medications</td>
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<td>§. Active malignancy and receiving chemotherapy</td>
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<td>‧. Autoimmune diseases requiring immunosuppressive therapy</td>
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<td>′. Advanced or untreated HIV infection</td>
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</table>

*Maximally vaccinated = completion of all recommended vaccines for age group, including booster

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 should carefully review concomitant medications, including over the counter and herbal products.
- If absolute contraindications, then refer for monoclonal antibody therapy only.
- 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 list below for drugs that are **absolute contraindications** for Paxlovid (not a comprehensive list)
  - PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance:
    - Alpha1-adrenoreceptor antagonist: alfuzosin
    - Analgesics: pethidine, piroxicam, propoxyphene
    - Antianginal: ranolazine
    - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:
- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John’s Wort (*hypericum perforatum*)

- See list below for drugs that may require extra monitoring or dose adjustments (not a comprehensive list)
  - Anticancer drugs: abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine
  - Anticoagulants: warfarin, rivaroxaban
  - Antifungals: voriconazole, ketoconazole, isavuconazole, itraconazole
  - Anti-HIV medications
  - Calcium channel blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine
  - Cardiac glycosides: digoxin
  - HMG-CoA reductase inhibitors: atorvastatin, lovastatin, simvastatin, rosuvastatin
  - Immunosuppressants: cyclosporine, tacrolimus, sirolimus
  - Systemic corticosteroids: betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone

The Paxlovid Fact Sheet and the Liverpool COVID-19 Drug Interactions website are resources to identify and manage DDIs.

For questions regarding drug-drug interactions that cannot be answered by the resources in the guideline or Liverpool, please contact the pharmacist in your patient care area or the pharmacist involved in the care of that patient regarding the specific drug interaction. Please consider the timing of this medication as the response back from the clinical pharmacist may not be immediate.

**Paxlovid Ordering Process**

- Check state of Michigan website for status of supply at select Meijer pharmacy ([Use Locator for Meijer Pharmacy](#))
- 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
- 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**
- In order to provide maximum access to therapeutics for high-risk patients, at this time for patients in whom drug-drug interactions are not an absolute contraindication, please also concomitantly place referral for COVID-19 mAb (i.e., do not want to delay review for sotrovimab infusion in patients who cannot obtain Paxlovid because supply ran out at pharmacy)
- Advise patients to fill the script and start taking the medication as soon as possible. If they are eligible for Paxlovid AND monoclonal antibody, tell them to take Paxlovid if the script is filled, and not to wait for a call regarding monoclonal antibody. They have similar efficacy in clinical trials.
- If e-prescribing is not possible, prescribe Paxlovid using [MDHHS prescription form](#)
  - Fill out, print, sign, and fax to Meijer Pharmacy of choice
Meijer will make filling this prescription a priority. During pharmacy business hours, prescriptions should 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. Meijer will 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 by having patient contact Meijer. 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 particular, this would include patients age 65-74, not maximally vaccinated, with a risk factor for progression to severe disease. Or, patients who are 75 or older, not maximally vaccinated, and are unable to get sotrovimab OR paxolvid.

**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>
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</thead>
<tbody>
<tr>
<td>1. Adults ≥18 years</td>
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<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 sotrovimab or Paxlovid due to supply constraints</td>
</tr>
<tr>
<td>5. Not Pregnant</td>
</tr>
<tr>
<td>6. One of the following:</td>
</tr>
<tr>
<td>a) Age ≥75 AND not maximally vaccinated*</td>
</tr>
<tr>
<td>b) Age ≥65 AND not maximally vaccinated* AND one of the following co-morbidities</td>
</tr>
<tr>
<td>I. Chronic respiratory disease (e.g., COPD, moderate or severe asthma (requires daily inhaled corticosteroid), bronchiectasis, CF, ILD)</td>
</tr>
<tr>
<td>II. Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)</td>
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<tr>
<td>III. Diabetes</td>
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<tr>
<td>IV. CKD (stage III; cannot prescribe if EGFR ≤30 mL/min)</td>
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<td>V. BMI ≥35</td>
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<tr>
<td>c) Immunosuppressed regardless of vaccination status:</td>
</tr>
<tr>
<td>I. Moderate or Severe Primary immunodeficiency</td>
</tr>
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<td>II. SOT on immunosuppressive medications</td>
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*Maximally vaccinated = completion of all recommended vaccines for age group, including booster
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
• Check state of Michigan website for status of supply: available at all Meijer pharmacy ([Use Locator for Meijer Pharmacy](https://meijerlocator.com)) and selected retail pharmacies in areas not served by Meijer
• 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](https://www.fda.gov) via email or patient portal
• 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
• If e-prescribing is not available, prescribe molnupiravir using [MDHHS prescription form](https://www.michigan.gov)  
  o Fill out, print, sign, and fax to Meijer Pharmacy of choice

Meijer will make filling this prescription a priority. During pharmacy business hours, prescriptions should 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. Meijer will 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 by having patient contact Meijer. Delivery will be made a priority but will likely result in a delay over pharmacy pick-up.

4. **Inhaled corticosteroids:**
Inhaled budesonide (800 mcg BID x14 days) and ciclesonide (320 mcg BID x30 days) have been studied in non-hospitalized adults with mild-moderate symptoms of COVID-19. The results of these studies do not demonstrate a consistent impact of inhaled corticosteroid therapy on time to recovery of COVID-related symptoms. Similarly, inhaled corticosteroid therapy reduced COVID-related emergency-department visits or hospitalizations in some studies but not others. As such, while we do not recommend inhaled corticosteroids as routine therapy, they may be considered on a case-by-case basis given some potential for benefit and a low risk of harm. Studies to date have not identified an optimal product or dose. While short-term inhaled corticosteroid therapy in COVID-19 patients has been shown to be relatively safe in studies to date, budesonide, ciclesonide, and fluticasone are all CYP3A4 substrates, and concomitant administration with potent CYP3A4 inhibitors such as azole antifungals, ritonavir, cobicistat, and clarithromycin (among others) may result in symptoms of corticosteroid excess. Such co-administration is not recommended.
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.