UTMC Guidance for COVID-19 Management

Updated 6/30/2022

Table 1: Overview of Treatment Recommendations Based on Hospitalization and Severity of Disease

Outpatient/Emergency Department	
COVID Disease Severity	**Treatment Recommendations**
Pre-exposure prophylaxis*	• ***Consider*** cilgavimab/tixagevimab
Mild illness with no risk factors*	• Self-management
Mild illness with risk factors*	• Initial tele-medicine evaluations with close follow-up • Consider in-person visit • ***Consider*** Paxlovid (nirmatrelvir/ritonavir) (**AIIa) [preferred, if clinically appropriate]** ^ • ***Consider*** molnupiravir **(CIIa)** • ***Consider*** bebtelovimab per UTMC protocol **(CIII)** • Do not give dexamethasone **(AIII)**
Moderate illness with/without risk factors* or severe illness	• Refer for in-person visit • ***Consider*** Paxlovid (nirmatrelvir/ritonavir) **[preferred, if clinically appropriate]** ^ • ***Consider*** molnupiravir **(CIIa)** • ***Consider*** bebtelovimab per UTMC protocol **(CIII)** • Do not give dexamethasone **(AIII)**

Hospitalized	
Does not require supplemental oxygen	• Supportive care • Daily labs to assess progression • Do not give dexamethasone **(AIIa)** • Use current standard dose thromboprophylaxis with LMWH
Requires supplemental oxygen	• Remdesivir 200 mg IV X 1 then 100 mg IV q24h X 4 days **(BIIa)** **or** • Remdesivir (dose above) plus dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge **(BIII)** **or** • If remdesivir cannot be used, consider dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge **(BI)** • Use current standard dose thromboprophylaxis with LMWH
Requires high-flow oxygen or non-invasive ventilation	• Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge **(AI)** **or** • Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge plus remdesivir **(BIII)** • Rapid increase in oxygen requirement (inclusive of HFNC ≥ 30 LPM [40% FiO2], NRB, or BIPAP) and systemic inflammation [as defined by inflammatory marker thresholds in Table 5]: ○ ***Consider*** tocilizumab **or** baricitinib **(BIIa)** • Use current standard dose thromboprophylaxis with LMWH

Hospitalized (continued)	
Requires mechanical ventilation	• Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge **(AI)** • For those within 24 hours of admission to ICU, ***consider*** tocilizumab **(BIIa)** • Use current standard dose thromboprophylaxis with LMWH

*****See High Risk Criteria for Progressing to Severe COVID-19 OR severe immune compromising conditions (cilgavimab/tixagevimab only)
^Paxlovid should be avoided in patients with significant drug-drug interactions, inadequate renal function, and inadequate hepatic function
Rating of Recommendations: A=Strong; B=Moderate; C=Optional
Rating of Evidence: I=1 or more RCT w/o major limitations; IIa=Other RCT or subgroup analysis; IIb=Nonrandomized trial or observational cohort; III= Expert opinion

Table 2: Oral Antiviral Agents for COVID-19

Individual Agents – *Prescriber must complete all EUA requirements*
Treatment – Patients Not Requiring Inpatient Hospitalization or Supplemental Oxygen
Paxlovid (Nirmatrelvir/ritonavir) **Dosing, based on eGFR:** • > 60 mL/min: 300mg of nirmatrelvir + 100mg ritonavir twice daily for 5 days • 30 – 60 mL/min: 150mg of nirmatrelvir + 100mg ritonavir twice daily for 5 days • < 30 mL/min: Use is not recommended – appropriate dosing has not been determined **Administration** • Nirmatrelvir/ritonavir may be taken with or without food • The tablets **may not** be crushed, chewed, or broken – please instruct patients to swallow the tablets whole • If a dose is missed, instruct patients to take their dose if they remember within 8 hours of the normal administration time – otherwise, please instruct them to skip that dose **Inclusion Criteria** • Mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40kg) with positive SARS-CoV-2 testing who are at high risk for progression to severe COVID-19, including hospitalization or death (see criteria in Table 3) • **NOTE:** Paxlovid should be initiated as soon as possible and within 5 days of symptom onset **Use is NOT authorized for the following:** • Patients requiring hospitalization due to severe or critical COVID-19 • Pre-exposure or post-exposure prophylaxis for COVID-19 • Use for longer than 5 consecutive days

Management Strategies for Drug-Drug Interactions

- **Consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are to receive Paxlovid**
- **Because Paxlovid is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed should NOT preclude the use of this medication**
- **Consider utilizing University of Liverpool COVID-19 Interaction Checker for streamlined information**

- **Clinically-Relevant Drug-Drug Interactions: Prescribe alternative therapy**
  - Anticonvulsants: Carbamazepine, phenobarbital, phenobarbital, phenytoin, primidone
  - Anti-infective Agents: Glecaprevir/pibrentasvir, rifampin, rifapentine
  - Immunosuppressants: Voclosporin
  - Cardiovascular Agents: Amiodarone, clopidogrel, disopyramide, dofetilide, dronedarone, eplerenone, flecainide, ivabradine, propafenone, quinidine
  - Neuropsychiatric Agents: Clozapine, lumateperone, lurasidone, midazolam (oral), pimozide
  - Pain Medications: Meperidine
  - Pulmonary Hypertension Medications: Sildenafil, tadalafil, vardenafil
  - Miscellaneous: lomitapide, fibanserin, bosentan, certain chemotherapeutic agents (see University Health Network/Kingston Guidelines and consult Oncology team), ergot derivatives lumacaftor/ivacaftor, St. John's wort, tolvaptan

- **Clinically-Relevant Drug-Drug Interactions: Consider temporarily holding concomitant medication, if clinically appropriate**
  - **It may be appropriate to hold certain medications listed below during and at least 2-3 days after treatment completion. If withholding is NOT clinically appropriate, use an alternative COVID-19 therapy**
  - Anticoagulants: Rivaroxaban (consult with primary or specialty provider first)
  - Anti-infective Agents: Erythromycin
  - BPH Medications: Alfuzosin, silodosin
  - Cardiovascular Agents: Aliskiren, ranolazine, vorapaxar, ticagrelor (consult with primary or specialty provider first)
  - Immunosuppressants: Everolimus, tacrolimus, sirolimus (see AST recommendations and consult prescribing physician first)
  - Lipid-modifying Agents:
    - Atorvastatin/rosuvastatin: withhold at the beginning of treatment and resume after completion of 5 day course
      - If co-administration is necessary, reduce dose to atorvastatin 10mg/rosuvastatin 5mg daily and resume usual dose 3 days after completing Paxlovid treatment
    - Lovastatin/simvastatin: withhold at least 12 hours before initiation of Paxlovid, during treatment, and at least 5 days after treatment completion
      - If statin therapy is necessary, lovastatin or simvastatin should be switched to an alternative statin
  - Migraine Medications: Eletriptan, rimegepant, ubrogepant
  - Neuropsychiatric Agents: Clonazepam, clorazepate, diazepam, estazolam, flurazepam, suvorexant, triazolam (consult specialty provider first)
  - Erectile Dysfunction Medications: Avanafil

- Respiratory Medications: Salmeterol (contact primary or specialty provider first)
- Miscellaneous: Certain chemotherapeutic agents (see University Health Network/Kingston Guidelines and consult Oncology team), colchicine, finerenone, flibanserin, naloxegol

- **Clinically-Relevant Drug-Drug Interactions: Consider temporary dose adjustment and monitor for adverse effects, if clinically appropriate**
  - **It may be appropriate to adjust the dosing of following medications during/shortly after the completion of Paxlovid. If it is NOT clinically appropriate, consider an alternative COVID-19 therapy**
  - **Please see University of Liverpool COVID-19 Interaction Checker for medication-specific recommendations**
  - Anticoagulants: Apixaban, dabigatran, edoxaban
  - Anti-infective Agents: Clarithromycin, itraconazole, ketoconazole, maraviroc, rifabutin
  - BPH Medications: Tamsulosin
  - Cardiovascular Agents: Cilostazol, digoxin, mexiletine
  - Corticosteroids (primarily metabolized by CYP3A: betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone
    - Co-administration (via any route) increases corticosteroid exposure and can increase the risk for Cushing's syndrome and adrenal suppression (low risk overall)
    - Consider alternative corticosteroids such as beclomethasone, prednisone, and prednisolone
  - Diabetes Medications: Saxagliptin
  - Erectile Dysfunction Medications: Sildenafil, tadalafil, vardenafil
  - Immunosuppressants: Cyclosporine (see AST recommendations and consult prescribing physician first)
  - Neuropsychiatric Agents: Alprazolam, aripiprazole, brexpiprazole, buspirone, cariprazine, chlordiazepoxide, clobazam, iloperidone, pimavanserin, quetiapine, trazodone (consult specialty provider first)
  - Pain Medications: Fentanyl, oxycodone, hydrocodone
  - Pulmonary Hypertension Medications: Riociguat
  - Miscellaneous: Certain chemotherapeutic agents ((see University Health Network/Kingston Guidelines and consult Oncology team), darifenacin, execaftor/tezacaftor/ivacaftor, eluxadoline, ivacaftor, tezacaftor/ivacaftor

- **Clinically-Relevant Drug-Drug Interactions: Pre-emptive dose adjustment is not required but may be considered, ensure patient is educated for potential adverse effects**
  - **Please see University of Liverpool COVID-19 Interaction Checker for medication-specific recommendations if dose adjustments may be needed**
  - Anticoagulants: Warfarin
  - Anti-infective Agents: Cobicistat or ritonavir-boosted antiretrovirals, isavuconazole, posaconazole, voriconazole
  - BPH Medications: Doxazosin, terazosin
  - Diabetes Medications: Glyburide
  - Cardiovascular Agents: Amlodipine, diltiazem, felodipine, nifedipine, sacubitril, valsartan, verapamil

- Neuropsychiatric Agents: Haloperidol, hydroxyzine, mirtazapine, risperidone, ziprasidone, zolpidem
- Pain Medications: Buprenorphine, hydromorphone, methadone, morphine, tramadol

Adverse Effects

- Adverse effects that occurred at a greater frequency (compared to placebo) in the available clinical trials include:
  - Dysgeusia (6%)
  - Diarrhea (3%)
  - Hypertension (1%)
  - Myalgia (1%)
- "COVID-19 Rebound" has been reported to occur between two and fourteen days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative
  - A brief return of symptoms may be part of the natural history of SARS-CoV-2 (COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status
  - This was not associated with the primary outcome of COVID-19-related hospitalization or death through day 28 following a 5-day treatment course
- Prescribing healthcare providers and/or their designees is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to this agent within 7 calendar days from the onset of the event(s). See the EUA Fact Sheet for Healthcare Providers for more information (www.COVID19oralRx.com)

Lagevrio (Molnupiravir)

Dosing

- Molnupiravir is dispensed in individual bottles containing forty 200mg capsules
  - Please dispense the capsules in the original container
- Patients should be instructed to take 800mg (four 200mg capsules) every 12 hours for 5 days
  - There are no recommended dose adjustments based on specific patient populations

Administration

- Administration
  - Molnupiravir may be taken with or without food
  - The capsules **may not** be opened, broken, or crushed – please instruct patients to swallow the capsules whole
  - If a dose is missed, instruct patients to take their dose if they remember within 10 hours of the normal administration time – otherwise, please instruct them to skip that dose

Inclusion Criteria

- Mild to moderate COVID-19 in adults patients (18 years of age or older) with positive SARS-CoV-2 testing 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 (see criteria in Table 3)

- **NOTE:** Lagevrio should be initiated as soon as possible and within 5 days of symptom onset

Use is NOT authorized for the following:

- Patients less than 18 years of age
- Patients requiring hospitalization due to severe or critical COVID-19
- Pre-exposure or post-exposure prophylaxis for COVID-19
- Use for longer than 5 consecutive days

Contraindications and Precautions

- No contraindications have been identified based on the limited available data on the emergency use of molnupiravir
- No drug-drug interactions have been identified based on the limited available data on the emergency use of molnupiravir
- The use of molnupiravir is **not recommended** during pregnancy; advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment **and** for 4 days after the last dose of molnupiravir
    - **If the decision is made to use molnupiravir during pregnancy, the prescriber must document that the known and potential effects of molnupiravir use during pregnancy, as outlined in the Fact Sheet for Patients and Caregivers, were discussed with the patient**
- Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir – individuals may consider pumping and discarding breast milk during this period, as well
- 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. The risk beyond 3 months after the last dose of molnupiravir is unknown
- Please see the EUA fact sheet (https://www.molnupiravir-us.com/patients/) for additional information, if required

Adverse Reactions

- Adverse effects that occurred during the available clinical trials include:
    - Diarrhea (2%)
    - Nausea (1%)
    - Dizziness (1%)
- Prescribing healthcare providers and/or their designees is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to this agent within 7 calendar days from the onset of the event(s). See the EUA Fact Sheet for Healthcare Providers for more information (https://www.molnupiravir-us.com/patients/)

Table 3: High Risk Criteria for Progressing to Severe COVID-19

- Obesity (BMI > 25)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease / currently receiving immunosuppressive treatment
- Cardiovascular disease or hypertension
- Chronic lung diseases (including moderate to severe asthma)
- Sickle Cell Disease
- Older age (≥ 65 years of age)
- Neurodevelopmental disorders
- Medical-related technological dependence
- Other medical condition or risk factor that may increase risk for progression to severe COVID-19

Table 4: Monoclonal Antibodies for COVID-19

Individual Agents – *Prescriber must complete all EUA requirements*
Pre-exposure Prophylaxis

Available Agent and Dosing Regimen
 	
Cilgavimab + tixagevimab (Evusheld)
• Initial Dosing: Cilgavimab 300mg IM injection + tixagevimab 300mg IM injection (gluteal)
• Repeat Dosing for Patients Receiving Initial Dose of cilgavimab 150mg + tixagevimab 150mg:
  ○ If first dose ≤ 3 months ago: administer additional dose of cilgavimab 150mg + tixagevimab 150mg
  ○ If first dose > 3 months ago: administer additional dose of cilgavimab 300mg + tixagevimab 300mg
• Repeat Dosing for Patients Who Received Initial Dose **OR** Previously Authorized Initial Dose Followed by Second Dose:
  ○ Cilgavimab 300mg IM injection + tixagevimab 300mg IM injection (gluteal) every 6 months timed from the date of the most recent dose

Inclusion Criteria

- **Not** currently infected with SARS-CoV-2 and have not had a known, recent exposure to an individual infected with SARS-CoV-2 **AND**
    - Has severe immune compromise (see criteria below) due to a medical condition or receipt of immunosuppressive medications or treatments **AND** may not mount an adequate immune response to COVID-19 vaccination **OR**
    - Vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine and/or its components

Exclusion Criteria

- < 12 years of age
- < 40 kg
- Individuals who have received COVID-19 vaccination in the previous 14 days

Severe immune compromising conditions:

- Patients within 1 year of receiving T- or B-cell depleting agents (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab, belatacept, anti-thymocyte globulin)
- Patients receiving Bruton tyrosine kinase inhibitors
- Post-hematopoietic cell transplant patients with chronic graft versus host disease or are taking immunosuppressive medications for another condition
- Patient with hematologic malignancies on active treatment
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant)
- Solid-organ transplant recipients with recent treatment (previous 1 year) for acute rejection with T- or B-cell depleting agents
- Severe combined immunodeficiencies
- Advanced or untreated HIV with a CD4 cell count < 50 cells/mm^3

Treatment and Post-exposure Prophylaxis

Available Agents and Dosing Regimens

Casirivimab + imdevimab - infusions of this agent are paused until further notice as it does not possess adequate activity against the Omicron variant

- Initial Dosing: Casirivimab 600mg IV plus imdevimab 600mg IV x 1
- Repeat Dosing for Ongoing Exposure: Casirivimab 300mg IV plus imdevimab 300mg IV (may be repeated every 4 weeks)

Bamlanivimab + etesevimab - infusions of this agent are paused until further notice as it does not possess adequate activity against the Omicron variant

- Bamlanivimab 700mg IV plus etesevimab 1400mg IV x 1

Sotrovimab - infusions of this agent are paused until further notice as it does not possess adequate activity against the Omicron subvariant, BA.2

- Sotrovimab 500mg IV x1

Bebtelovimab

- Bebtelovimab 175mg IV x1

Inclusion Criteria

- Positive SARS-CoV-2 test
- Symptom onset within last 7 days
- High risk for progressing to severe COVID-19 (see criteria in Table 3)
- **Per bebtelovimab EUA criteria, bebtelovimab should be considered when alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate (i.e., drug-drug interactions, inadequate renal or hepatic function)**

Exclusion Criteria

- Current hospitalization for COVID-19
- < 12 years of age
- < 40 kg
- Requiring supplemental oxygen (or if on chronic oxygen, requiring an increase in baseline oxygen flow rate) due to COVID-19

Ordering Process

- Outpatient: Provider submits paper order form to BOP Room (Phone: 419-383-4432) for review and processing
- Inpatient: Provider submits paper order form to Inpatient Pharmacy (Fax: 419-383-2828) for review and processing
    - **If patient is currently admitted to UTMC, it must be for a diagnosis other than COVID-19 AND approval from Infectious Diseases is required**

Table 5: Suggested Laboratory and Vital Sign Monitoring

Laboratory Parameters	**Vital Sign Monitoring**

• D-dimer (>0.49 mcg/ml)
• Creatine phosphokinase (> 2x upper limit of normal [ULN])
• C-reactive protein (>75 mg/L)
• Lactate dehydrogenase (>271 U/L)
• Troponin (elevated)
• Ferritin (>336 ng/L)
• Complete blood count with differential
  ○ Lymphocytes (< 0.8 k/µL)
• Complete metabolic panel
  ○ LFTs generally elevated
	• Respiratory rate >24 breaths/min
	• Heart rate >125 bpm
	• SpO2 <94% on room air
	• PaO2/FiO2 <300 mmHg

Table 6: Inpatient COVID-19 Therapies

Convalescent Plasma
• Only to be used in the setting of clinical trial
Intravenous Immune Globulin (IVIG)
• Only to be used in the setting of clinical trial
Remdesivir (Pharmacy to dose)
Dosing Regimen: • Day 1: 200 mg IV x1 • Days 2-5: 100 mg IV every 24 hours x 4 doses **Inclusion Criteria** • Positive SARS-CoV-2 test • Oxygen saturation ≤ 94% on room air OR requiring supplemental oxygen   ○ If patient requires oxygen supplementation at baseline, there must be an increased requirement from baseline • Day 14 of illness or earlier (including symptoms prior to admission) • ALT < 10x ULN **Exclusion Criterion** • DNRCC

Precaution

- Creatinine clearance (CrCl) < 30 mL/min: the pharmacokinetics of remdesivir have not been evaluated in patients with CrCl < 30 mL/min. The risk of toxicity in these patients is low and the benefit of remdesivir likely outweighs this risk. Consider contacting Infectious Diseases Physician or Antimicrobial Stewardship Pharmacist (Matt Rico) if there are circumstances where you are concerned with adverse effects or remdesivir accumulation (e.g., peritoneal dialysis, anuria)

Laboratory Monitoring

- Pharmacy will order daily comprehensive metabolic panel to evaluate baseline renal function and daily liver function while receiving remdesivir

Infusion-related Reactions (e.g., hypotension, hypertension, tachycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, shivering)

- Slow infusion rate, with a maximum infusion time of up to 120 minutes, to potentially prevent these signs and symptoms. If clinically significant infusion-related reactions occur, immediately discontinue and initiate appropriate treatment

Tocilizumab (requires Infectious Diseases approval) - *Prescriber must complete all EUA requirements*

Dosing Regimen:

- Doses will be rounded based on weight according to the scale below, with a single dose maximum of 800 mg:
  - < 40 kg: contact pharmacy
  - ≥ 40 – 60 kg: 400 mg IV x1
  - > 60 – 85 kg: 600 mg IV x1
  - > 85 kg: 800 mg IV x1
- A second dose is not recommended due to increased risk of possible secondary infection and lack of proven benefit

Inclusion Criteria

- Positive SARS-CoV-2 test
- Receiving systemic corticosteroids
- Admission within previous 72 hours
- Rapidly increasing oxygen requirement to keep saturation adequate (inclusive of HFNC ≥ 30 LPM [40% FiO2], NRB, or BIPAP) ***OR*** within 24 hours of mechanical ventilation
- CRP >75 mg/L (if available)
- Clinical deterioration is not from a secondary infection/process

AVOID use in the follow scenarios:

- Uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- AST or ALT > 5x ULN
- ANC < 500/mm^3
- Platelet count < 50,000/mm^3
- If status is not known, order HIV, HBV, and IGRA (QuantiFERON). Also order strongyloides IgG (for patients with epidemiological risk factors).

Baricitinib (requires Infectious Diseases approval - to be used only if tocilizumab is unavailable) - *Prescriber must complete all EUA requirements*

Laboratory Parameters

- CBC with differential and CMP should be evaluated prior to receiving first dose

Dosing Regimen

- eGFR ≥ 60 mL/min/1.73m^2: 4 mg PO once daily
- eGFR 30 to < 60 mL/min/1.73 m^2: 2 mg PO once daily
- eGFR 15 to < 30 mL/min/1.73 m^2: 1 mg PO once daily
- eGFR < 15 mL/min/1.73m^2: Not recommended
- In patients who cannot swallow tablets, please **contact pharmacy** for reconstitution instructions

Inclusion Criteria

- Positive SARS-CoV-2 test
- Receiving systemic corticosteroids
- Admission within previous 5 days
- Rapidly increasing oxygen requirement to keep saturation adequate (inclusive of HFNC ≥ 30 LPM [40% FiO2], NRB, or BIPAP)
- CRP >75 mg/L (if available), D-dimer > 0.49 mcg/mL, ferritin > 336 ng/mL, **OR** lactate dehydrogenase > 271 U/L
- Clinical deterioration is not from a secondary infection/process

AVOID use in the following scenarios:

- History of DVT/PE
- Uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- AST or ALT > 5x ULN
- ANC <500/mm^3 or ALC <200/mm^3
- eGFR < 15 mL/min
- High risk for GI perforation (chronic NSAID use, recent or active diverticulitis/diverticulosis, chronic steroid use, peptic ulcer disease in the last 6 months)