Outpatient COVID-19 Therapeutics Overview

General Information

- Outpatient COVID-19 therapeutic agents, FDA approval status, and availability at Parkland are listed in Table 1
- Many current therapeutic agents are authorized by the US Food & Drug Administration (FDA) under an emergency use authorization (EUA). Specific EUA requirements are summarized in the tip sheets created for each agent

Table 1. Availability of Current Agents

Presentation	Type	FDA Authorized Options	FDA Approval	Parkland Supply
Asymptomatic; COVID (-); with no recent exposures	**Prevention**	COVID-19 vaccines	Pfizer – Yes Others – EUA	Yes
		Tixagevimab/Cilgavimab (Evusheld)	EUA	Limited; prioritized by risk for progression to severe disease
Asymptomatic; COVID(-); with recent exposure and high-risk for progression	**Post-Exposure Prophylaxis**	Casirivimab/Imdevimab (Regeneron) Bamlanivimab/Etesevimab	EUA	On hold; no activity against Omicron variant
Mild to moderate symptoms; not hospitalized; COVID (+); and high-risk for progression	**Treatment**	Casirivimab/Imdevimab (Regeneron) Bamlanivimab/Etesevimab	EUA	On hold; no activity against Omicron variant
		Sotrovimab (Xevudy) Nirmatrelvir/Ritonavir (Paxlovid) Molnupiravir (Lagevrio)	EUA	Limited; prioritized by risk for progression to severe disease
		Remdesivir (Veklury)	Yes	Yes, only for inpatient use at this time

Pre-exposure Prophylaxis

Overview of Evusheld for pre-exposure prophylaxis of COVID-19

- Tixagevimab and Cilgavimab are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2
- PrEP is not a substitute for vaccination in those whom COVID-19 vaccination is recommended
- In individuals who received a COVID-19 vaccine, delay Evusheld administration for at least 2 weeks
- No guidance is available regarding optimal timing of the COVID-19 vaccine after receiving Evusheld

Which patients are authorized to receive Evusheld?

- Evusheld is authorized as pre-exposure prophylaxis for the prevention of COVID-19 in adult and pediatric individuals (≥ 12 years old & weight ≥ 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
    - Have moderate to severe immune compromise **and** may not mount an adequate immune response to COVID-19 vaccination

      OR
    - For whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine and/or its components

How is Evusheld administered and are there special monitoring requirements?

- Tixagevimab and Cilgavimab are administered separately as two 1.5 mL (150 mg) IM injections
- IM injections should use two different injection sites, preferably one in each of the gluteal muscles
- Patients are recommended to be observed for at least 1 hour after the injections

What screening tests need to be completed prior to Evusheld administration?

- **COVID-19 antibody screening** should be performed ≤ 7 days prior to Evusheld administration
- **COVID-19 viral PCR testing** should be performed ≤ 24 hours prior to Evusheld administration
- Both tests should be negative to rule out active immunity as well as active infection, respectively (Table 2)
    - If either test result is positive, the patient should not receive Evusheld

Table 2. Interpreting Screening Laboratory Results

Lab	**Results**			
COVID-19 antibody screen	**-**	**+**	**-**	**+**
COVID-19 viral PCR test	**-**	**-**	**+**	**+**
Candidate for Evusheld?	**Yes**	No	No	No

How to obtain Evusheld at Parkland

- Patients who meet FDA EUA criteria will be further prioritized based on risk categories
- Outpatient Requests
    - Evusheld is orderable via an Epic Therapy Plan and medications are loaded in Pyxis in Oncology, Transplant & HIV clinics
    - All other clinic areas: email Steven Schultz or Jessica Ortwine
- Inpatient Requests
    - Should be entered using the standard non-formulary medication review process

Post-exposure Prophylaxis

Which medications are approved for post-exposure prophylaxis of COVID-19?

- Both Bamlanivimab/Etesevimab and Casirivimab/Imdevimab have been granted Emergency Use Authorization for prevention of COVID-19 disease in in adults and pediatric individuals (≥ 12 years old & weight ≥ 40 kg) who are not currently infected with SARS-CoV-2 and who are:
    - Not fully vaccinated **or** not expected to mount an adequate immune response to COVID-19 vaccination **and**
    - Have been exposed to an individual known to be infected with SARS-CoV-2 consistent with close contact criteria **or** who are at high-risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons)

How to obtain agents for PEP at Parkland

- Infusions of monoclonal antibodies for PEP are currently on hold due lack of activity of both authorized agents (Bamlanivimab/Etesevimab or Casirivimab/Imdevimab) against the Omicron variant

Treatment

Which patients are eligible for outpatient COVID-19 treatment?

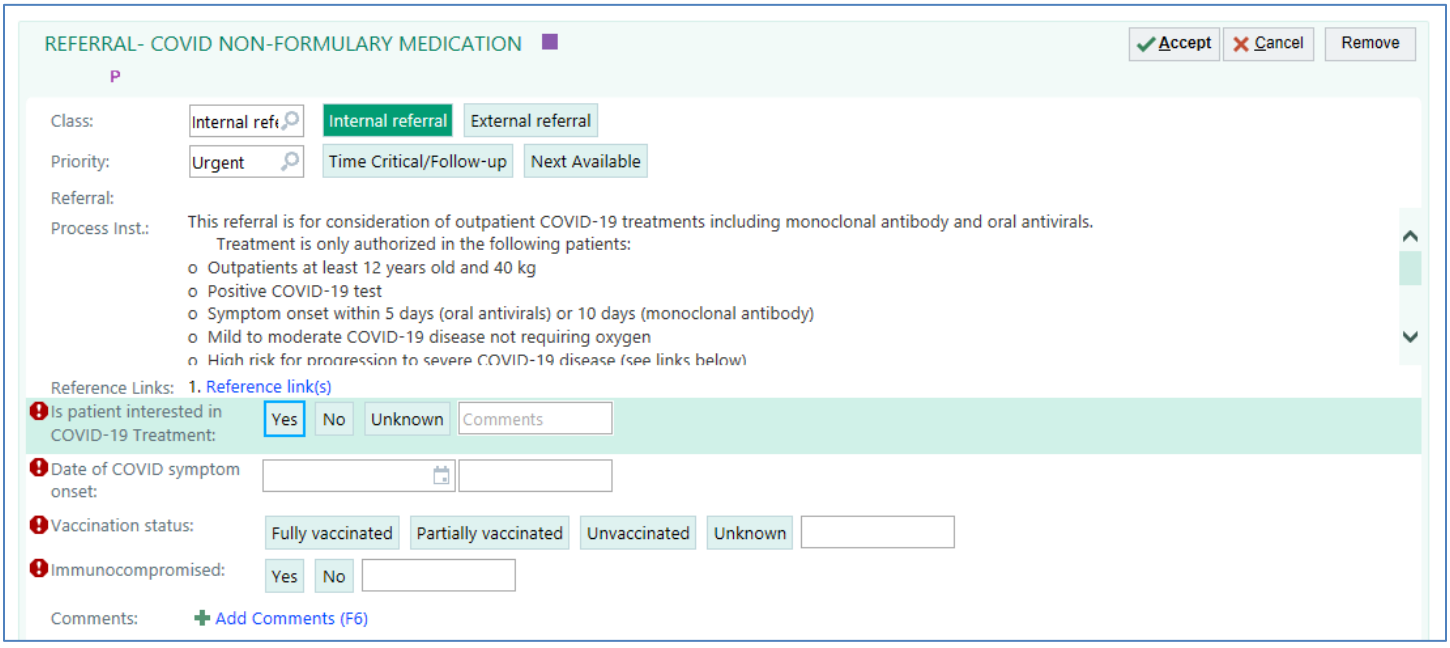
- Outpatients with mild to moderate symptoms of PCR-confirmed COVID-19 disease who are:
  - Within 10 days of initial symptom onset (≤ 5 days for orals; ≤ 10 days for mAbs) **and**
  - High-risk for progression to severe COVID-19, including hospitalization or death
- Patients must meet at least one high-risk criteria such as: age ≥ 65; BMI ≥ 25; pregnancy; diabetes; chronic kidney disease; immunosuppressed; cardiovascular disease or hypertension; chronic lung disease; sickle cell disease; neurodevelopmental disorders or other medically complex conditions; medical-related technological dependence
  - Refer to CDC website for full list of high-risk medical conditions and factors
- While these therapies remain in short supply, additional eligibility criteria have been added based on tiered risk categories 1 and 2 adapted from the NIH COVID-19 Treatment Guidelines

Which patients are NOT authorized to receive outpatient treatments?

- Patients hospitalized due to COVID-19 **or**
- Patients requiring oxygen support (in excess of their baseline) due to COVID-19

How to obtain outpatient COVID-19 treatment agents from Parkland pharmacy

- Ordering provider should confirm that patient meets all EUA eligibility criteria (see above)
  - While supplies are limited, patients must additionally meet NIH Tier 1 or Tier 2 criteria (see Appendix A)
- Treatment requests should be placed using the COVID Non-Formulary Medication referral



- Referrals will be reviewed by a clinical pharmacist during Weekdays only (Figure 1)
- The most appropriate therapy will be selected based on time from symptom onset, clinical efficacy, patient-specific characteristics, medication supply, and logistical barriers (Figure 2)

How to obtain outpatient COVID-19 treatment agents from an external pharmacy

- For monoclonal antibody infusions (i.e. Sotrovimab), refer patients to one of the regional infusion clinics
- For oral therapies (i.e. Molnupiravir, Paxlovid), use the COVID-19 Public Therapeutic Locator
  - Search "Find in this Dataset" by preferred geographic location (i.e. zip code or city)

- Website is updated every 24-48 hours, consider calling the pharmacy to confirm medication supply

Table 3. Summary of COVID-19 Outpatient Treatment Options

	Xevudy (Sotrovimab)	Paxlovid (Nirmatrelvir/Ritonavir)	Lagevrio (Molnupiravir)	Veklury (Remdesivir)
Dose	500 mg IV x 1	300 mg Nirmatrelvir + 100 mg Ritonavir (2 pink tab + 1 white tab) PO BID x 5 days	800 mg (4 x 200 mg caps) PO BID x 5 days	200 mg IV x 1, then 100 mg IV daily x 2 days
Treatment Window	≤ 10 days from symptom onset	≤ 5 days from symptom onset	≤ 5 days from symptom onset	≤ 7 days from symptom onset
Exclusions	• < 12 years old • 12-17 years old and < 40 kg	• < 12 years old • 12-17 years old and < 40 kg • Serious CYP3A4 drug interactions* • Severe renal impairment (eGFR < 30) • Dialysis dependent • Severe hepatic impairment (class C)	• < 18 years old • Pregnancy • Breastfeeding	• < 12 years old • 12-17 years old and < 40 kg • ALT > 10x ULN at baseline or within the past 3 months
Risk vs. Benefit Discussion Needed		• Untreated or uncontrolled HIV infection** • Pre-existing liver disease, liver enzyme abnormalities, or hepatitis		• Pre-existing liver disease, liver enzyme abnormalities, or hepatitis
Dose Adjustments	None	• eGFR ≥ 30 to < 60: reduce dose to 150 mg Nirmatrelvir + 100 mg Ritonavir (1 pink tab + 1 white tab) PO BID x 5 days • eGFR < 30: Not recommended	None	None
Monitoring	• Observe at least 1 hour post-infusion for infusion-related or hypersensitivity reactions	• Drug interactions		• Observe at least 15-30 minutes post-infusion for infusion-related or hypersensitivity reactions
Adverse Events	• Hypersensitivity (2%), diarrhea (2%), rash (1%)	• Dysgeusia (6%), diarrhea (3%), hypertension (1%), and myalgia (1%)	• Diarrhea (2%), dizziness (1%), nausea (1%)	• Elevated ALT (2-7%), elevated AST (3-6%), nausea (3-7%)
Key Clinical Efficacy Findings	• Significantly decreased rates of hospitalization or all-cause mortality by day 29 compared to placebo (1% vs. 6%; P < 0.001) • **Relative risk reduction: 79%** • No deaths among patients receiving Sotrovimab; 2 deaths in placebo group	• Significantly decreased rates of hospitalization or all-cause mortality through day 28 compared to placebo (0.8% vs. 6.3%; P < 0.0001) • **Relative risk reduction: 88%** • No deaths among patients receiving Paxlovid; 12 deaths in placebo group	• Significantly decreased rates of hospitalization or all-cause mortality by day 29 compared to placebo (6.8% vs. 9.7%; P = 0.0218) • **Relative risk reduction: 30%** • 1 death among patients receiving Molnupiravir; 9 deaths in placebo group	• Significantly decreased rates of hospitalization or all-cause mortality by day 29 compared to placebo (0.7% vs. 5.3%; P = 0.008) • **Relative risk reduction: 87%** • No deaths in any study patient

*****Ritonavir is a CYP3A4 inhibitor which slows the metabolism (increases concentrations) of drug substrates that use the CYP3A4 metabolic pathway; refer to the NIH guidelines as well as the Liverpool Drug Interactions Website and EUA Fact sheet for information regarding specific drug-drug interactions

- Patients already on Ritonavir- or Cobicistat-containing HIV or HCV treatment regimens are recommended to continue those regimens as prescribed while on Paxlovid

**Ritonavir is an HIV-1 protease inhibitor; there may be a risk of HIV-1 developing resistance in patients with uncontrolled or undiagnosed HIV-1 infection

Figure 1. Outpatient COVID-19 Treatment Workflow

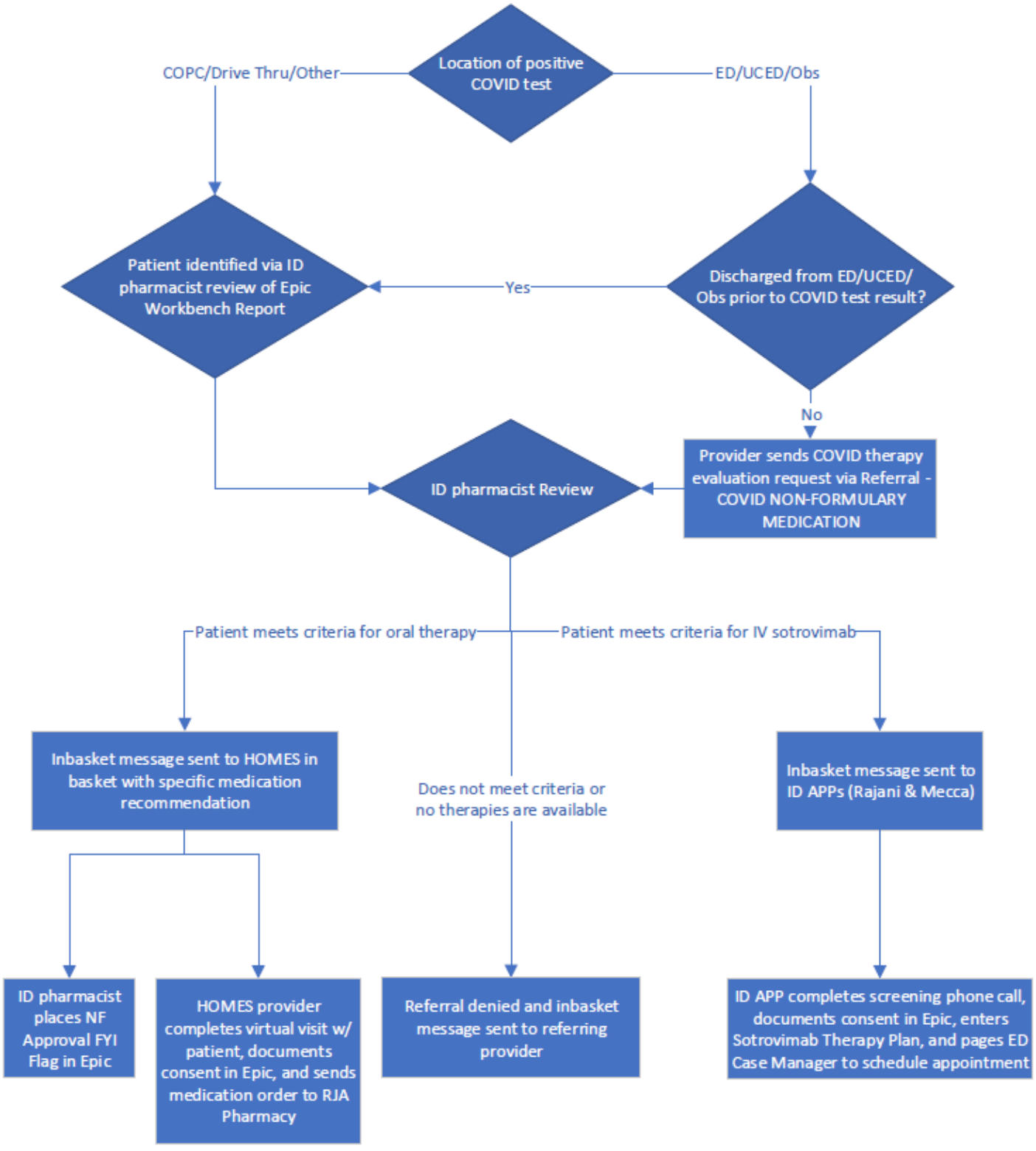
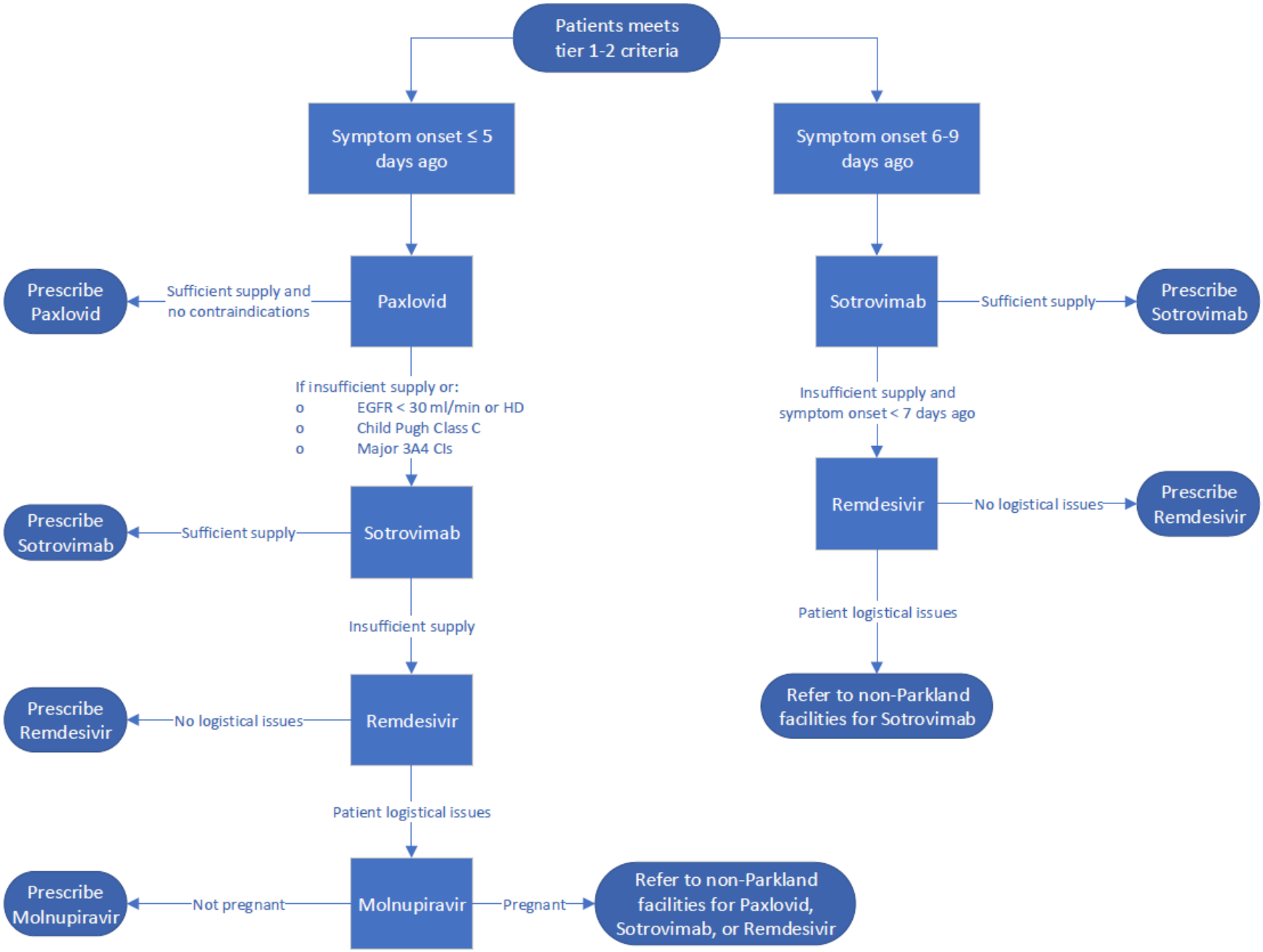


Figure 2. Outpatient COVID-19 Treatment Decision Algorithm



Medications Not Recommended for the Prophylaxis or Treatment of COVID-19

- Off-label use of the following medications is not recommended at this time due to lack of well-designed clinical trial data demonstrating benefit:
    - Antibiotics (unless evidence of bacterial co-infection)
    - Atovaquone
    - Colchicine
    - Convalescent plasma
    - Darunavir with ritonavir or cobicistat
    - Famotidine
    - Fluvoxamine
    - Hydroxychloroquine
    - Ivermectin (ONLY if needed for prophylaxis or treatment of Strongyloides, limited to 1-2 doses)
    - IVIG
    - Lopinavir with ritonavir
    - Mefloquine
    - Ondansetron
    - Ribavirin
    - Vitamin C
    - Vitamin D
    - Zinc
- The Antimicrobial Stewardship subcommittee and Pharmacy & Therapeutics (P&T) Committee will continue to review the data for these agents and update this list as new evidence becomes available

Additional Resources

- Parkland Provider Tip Sheets
    - In process
- Provider Fact Sheets
    - Evusheld
    - Sotrovimab
    - Paxlovid
    - Molnupiravir
- For more detailed information, please refer to the IDSA and NIH guidelines

Appendix A. NIH-Based Tiered Criteria for Outpatient COVID-19 Treatment

Tier	Criteria
Tier 1	Severely immunocompromised* regardless of vaccine status OR ≥ 75 years **and** not fully vaccinated** OR ≥ 65 years **and** ≥ 1 clinical risk factor for severe disease **and** not fully vaccinated
Tier 2	< 65 years **and** ≥ 1 clinical risk factor for severe disease **and** not fully vaccinated OR Pregnant **and** not fully vaccinated
Tier 3	≥ 75 years **and** fully vaccinated OR ≥ 65 years **and** ≥ 1 clinical risk factor **and** fully vaccinated OR Pregnant **and** ≥ 1 clinical risk factor **and** fully vaccinated
Tier 4	< 65 years **and** ≥ 1 clinical risk factor **and** fully vaccinated

*Severely immunocompromised as defined in NIH Guidance

**Full vaccination is currently considered to be 2 doses of Pfizer, 2 doses of Moderna, or 1 dose of J&J

NIH-Defined Immunocompromising Conditions

- Patients within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- 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 for acute rejection with T or B cell depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm3

Common Clinical Risk Factors

- Age > 65 years of age
- BMI > 25 or BMI > 85th percentile for age/gender based on CDC growth charts if age 12-17
- Diabetes
- Chronic kidney disease
- Immunosuppressed
- Cardiovascular disease
- Hypertension
- COPD/asthma, reactive airway or other chronic respiratory disease requiring drug therapy
- Sickle cell disease
- Congenital and acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- Pregnancy