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**Clinical Guidance on Therapeutics for COVID-19**  
*Issued January 28, 2022*

- **Remdesivir now approved by FDA for use in mild-to-moderate COVID in outpatients**
- **FDA has determined that bamlanivimab/etesivimab and casirivimab/imdevimab (REGEN-COV) are not currently authorized for use due to predominance of Omicron variant**
- **Updated treatment recommendations for COVID-19 therapeutics**
- **Updated website for access to COVID-19 therapeutics**

The purpose of this document is to provide guidance to health care providers on the use of therapeutics to treat individuals with mild-to-moderate COVID-19 who do not require hospitalization.

**Providers should ensure that they are reading the most current version of this guidance as recommendations frequently change.**

At present, there are two general classes of treatment for mild-to-moderate COVID-19: monoclonal antibodies (mAb) and antivirals. **These therapies are allocated to states by the federal government. Currently, supply of both therapy types is extremely constrained. Additionally, due to the presence of the Omicron variant and consistent with federal guidance, two mAb therapies, bamlanivimab/etesivimab and casirivimab/imdevimab, should not be used at this time.**

**Treatment of COVID-19 with monoclonal antibody therapy**

There is currently only one anti-SARS-CoV-2 monoclonal therapy which is may be used for treatment of COVID-19 pursuant to an Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA): [sotrovimab](#). On January 24, 2022, the FDA revised the EUAs for [casirivimab/imdevimab \(REGEN-COV\)](#), and [bamlanivimab/etesivimab](#). They are not currently authorized because the dominant Omicron variant is not susceptible to these agents. These therapies may be authorized for use in the future should the presence of the Omicron variant subside.

Monoclonal antibody therapy decreases the risk of severe disease from COVID-19 between 70% and 85% in clinical trials. Treatment with sotrovimab is indicated for treatment of COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who meet EUA criteria including:

1. Individuals who have mild-to-moderate, symptomatic COVID-19, with at least one symptom including but not limited to fever, chills, body aches, new loss of taste or smell, nausea,

vomiting, cough, sore throat, nasal congestion, runny nose, diarrhea, shortness of breath, headache

2. Symptom onset within the past 10 days and received a positive COVID-19 test (antigen or molecular) within the past 10 days
3. Individuals who have at least one risk factor for progression to severe disease or death from COVID-19, including but not limited to age  $\geq$  65 years old, pregnancy, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressive treatment, cardiovascular disease, hypertension, chronic lung disease, sickle cell disease neurodevelopmental disorder, medical-related technological dependence, obesity BMI  $>$  25 or above 85<sup>th</sup> percentile for age/gender), other medical conditions that place one at high risk for severe disease<sup>1</sup>

SARS-COV-2 variants may have different susceptibilities to monoclonal antibodies, which may influence choice of agent. Sotrovimab is currently the only mAb product for treatment of COVID-19 when Omicron is dominant and is the only mAb product which may be used.

Monoclonal antibodies are not authorized for individuals who are hospitalized due to COVID-19 or who require supplemental oxygen for COVID-19. If using home oxygen therapy, mAb therapy is not authorized if the oxygen dose has increased following start of symptoms/positive test for COVID-19. Individuals who have a history of allergic reaction (hives, facial swelling, difficulty breathing, anaphylaxis) following mAb therapy should not receive additional mAb doses.

For treatment of mild to moderate COVID-19, the authorized dose of [sotrovimab](#) is 500 mg, administered as a single intravenous infusion.

Patients should receive monoclonal antibodies in a setting equipped to manage anaphylaxis and should be observed for 1 hour following infusion.

### **Prophylaxis of COVID-19 with monoclonal antibody therapy**

The long-acting mAb [tixagevimab/cilgavimab EVUSHELD](#) is authorized for pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older and weighing at least 40 kg) who meet EUA criteria including:

1. Individuals 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
2. Individuals who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination including but not limited to active treatment for malignancy, receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor T cell or hematopoietic stem cell transplant, moderate or severe primary immunodeficiency, advanced or untreated HIV, treatment with immunosuppressive or immunomodulating agents
3. Individuals for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction.

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<sup>1</sup> <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>

Tixagevimab/cilgavimab confers protection against the Omicron variant and should be used in an environment when Omicron variant is dominant.

For pre-exposure prophylaxis, the authorized dose of [tixagevimab/cilgavimab](#) is 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate intramuscular injections, ideally in the gluteal or vastus lateralis muscle.

[Casirivimab/imdevimab](#) and [bamlanivimab/etesevimab](#) were previously authorized for use as postexposure prophylaxis to be administered as soon as practicable after an exposure (with no maximum timeframe). **Given that Omicron is now the dominant variant in Massachusetts, and these agents have reduced activity against Omicron, their use for post-exposure prophylaxis is not authorized at this time.** [Sotrovimab](#) is not authorized for post-exposure prophylaxis.

### **Treatment of COVID-19 with remdesivir**

[Remdesivir \(VEKLURY\)](#) is an FDA-approved antiviral therapy for use in adult and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization and in outpatients with mild-to-moderate COVID-19 within seven days of symptom onset in patients at risk of progression to severe disease. The FDA has also issued an EUA to permit the use of remdesivir for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg who are hospitalized or not hospitalized and have mild-to-moderate COVID-19 with risk factors for progression to severe disease.

For non-hospitalized adult and pediatric patients 12 years of age and older and weighing at least 40 kg, remdesivir is administered through a series of three daily intravenous infusions (200 mg, 100 mg, 100 mg). See the [EUA Fact Sheet](#) for information on dosing for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg.

Remdesivir is expected to retain activity against the Omicron variant.

### **Treatment of COVID-19 with oral antiviral therapy**

The oral antiviral therapy [nirmatrelvir co-packaged with ritonavir \(PAXLOVID\)](#) is available under FDA EUA for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients (12 years of age and older and weighing at least 40 kg).

Nirmatrelvir is a protease inhibitor antiviral agent with activity against SARS-CoV-2. It is co-packaged with ritonavir, an HIV protease inhibitor used to increase nirmatrelvir plasma concentrations. Clinical trials have shown nirmatrelvir boosted with ritonavir (nirmatrelvir/r) reduced the risk of COVID-19 related hospitalization or death by 89% compared to placebo in individuals with mild-to-moderate COVID-19 when given within five days of symptom onset.

Based on FDA approval, nirmatrelvir/r is indicated for treatment of COVID-19 in individuals who meet the following two criteria:

1. Individuals who have mild to moderate COVID-19 and a positive viral direct SARS-CoV-2 viral test (molecular or antigen)
2. Individuals who are at high risk for progression to severe COVID-19.<sup>1</sup>

Nirmatrelvir/r should be taken as soon as possible after the diagnosis of COVID-19, and within five days of symptom onset.

Nirmatrelvir/r is not authorized for treatment in patients requiring hospitalization due to COVID-19, pre-exposure or post-exposure prophylaxis or for use longer than five consecutive days.

The dose of nirmatrelvir/r is 300 mg of nirmatrelvir with 100 mg of ritonavir twice daily for five days. A single five-day course will be dispensed at one time in a blister pack. Nirmatrelvir/r should be avoided in individuals on medications not compatible with protease inhibitors or that cannot be temporarily held. Nirmatrelvir/r dose should be reduced for moderate renal impairment (eGFR  $\geq 30$  to  $< 60$  mL/min). Nirmatrelvir/r is not recommended in patients with severe renal impairment (eGFR  $< 30$  mL/min) or severe hepatic impairment (Child-Pugh Class C).

Extremely limited allocations of nirmatrelvir/r are expected through early 2022.

A second oral antiviral therapy, [molnupiravir](#), is available under FDA EUA for the treatment of mild-to-moderate COVID-19 in adult patients.

Molnupiravir is a nucleoside analog antiviral agent active against SARS-CoV-2. Clinical trials have shown molnupiravir to reduce severe disease by 30% compared to placebo in individuals with mild-to-moderate COVID-19 when given within 5 days of symptom onset.

Molnupiravir is indicated for treatment of COVID-19 in individuals who meet the following three criteria:

1. Individuals who have mild to moderate COVID-19 and a positive viral direct SARS-CoV-2 viral test (molecular or antigen)
2. Individuals who are at high risk for progression to severe COVID-19.<sup>1</sup>
3. Individuals for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Molnupiravir should be taken as soon as possible following a diagnosis of COVID-19, and within five days of symptom onset.

Molnupiravir is not authorized for treatment in patients less than 18 year of age, patients requiring hospitalization due to COVID-19, as pre-exposure or post-exposure prophylaxis or for use longer than five consecutive days.

The dose of molnupiravir is 800 mg (four 200 mg capsules) twice daily for five days. A single course of 40 pills will be dispensed at one time.

The use of molnupiravir is not recommended during pregnancy. Individuals of childbearing potential should be advised to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of molnupiravir. Breastfeeding is not recommended during treatment and for four days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for four days after the last dose of molnupiravir. Sexually active male individuals with partners of childbearing potential should be advised to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir.

Limited allocations of molnupiravir are expected through early 2022.

Prescribers of nirmatrelvir/r or molnupiravir must comply with the conditions of any EUA which is issued, and particularly should discuss potential risks and benefits of oral antiviral therapy with their patients prior to prescribing.

### **Recommendations**

Nirmatrelvir/r should be prioritized for individuals with highest risk (Tier 1 - 3) for severe COVID-19. Tiers are based on four elements: age, vaccination status, immune status and other clinical risk factors, consistent with [National Institutes of Health COVID-19 treatment guidelines](#) (Table). If nirmatrelvir/r is indicated for the highest risk individuals but not available or contraindicated, mAb therapy (sotrovimab) or remdesivir should be considered. Molnupiravir may be used if all other therapies are not available. Individuals with COVID-19 and risk factors for severe disease who are not classified as highest risk (Tier 1 - 3) and who are within 5 days of the onset of symptoms should be treated with remdesivir or molnupiravir if remdesivir is not available.

**Table: Treatment recommendations for mild to moderate COVID-19 when supplies of sotrovimab and oral antivirals are limited.**

		Recommendation	
Tier	Patient characteristics*	Within 5 days of symptom onset***	Between 5 – 10 days of symptom onset
1	Moderate to severe immunosuppression	Nirmatrelvir/r preferred. If nirmatrelvir/r not available or feasible, sotrovimab or remdesivir preferred. Molnupiravir may be used if other therapies not available or feasible. ****	Sotrovimab
	Not fully vaccinated and age $\geq 75$ years		
	Not fully vaccinated and age $\geq 65$ years plus additional risk factor		
2	Not fully vaccinated and age $\geq 65$		
	Not fully vaccinated and age $< 65$ plus additional risk factor		
3	Vaccinated** and age $\geq 75$		
	Vaccinated and age $\geq 65$ years plus additional risk factor		
4	Vaccinated and age $\geq 65$ years	Remdesivir preferred. Molnupiravir may be used if other therapies not available or feasible.	
	Vaccinated and age $< 65$ plus additional risk factor		

\*Clinical risk factors include cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt of immunosuppressive medications, obesity (body mass index  $\geq 30$ ), pregnancy, and sickle cell disease. For additional information on

medical conditions and other factors that are associated with increased risk for progression to severe COVID-19, see the CDC webpage [People With Certain Medical Conditions](#). **The likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities. Medical conditions or other factors (e.g., social determinants of health) not listed may also be associated with high risk for progression to severe COVID-19. Sotrovimab and nirmatrelvir/r may be considered for patients with multiple high-risk conditions or comorbidities and factors that are not listed in the EUAs. The decision to use mAb or antivirals for a patient should be based on an individualized assessment of risks and benefits. Use of mAb or antivirals that departs from tiering recommendations is permissible if based on clinical judgement.**

\*\*Vaccinated individuals who have not received a COVID-19 vaccine booster dose are at higher risk for severe disease.

\*\*\*Remdesivir may be used within seven days of symptom onset.

\*\*\*\*Use of molnupiravir is not recommended during pregnancy.

Other considerations for provision of oral agents to those who might otherwise receive monoclonal antibodies or remdesivir:

- Monoclonal antibody or remdesivir infusion is not available or subject to inordinate delay
- Patient unwillingness to receive intravenous mAb or remdesivir
- Likelihood of SARS-CoV2 variant not susceptible to available monoclonal antibody

Decisions about which eligible patients receive the drugs should be based on the clinical judgement of the providers, consistent with the terms of the relevant EUA and with this guidance.

Provider criteria for COVID-19 therapeutics use should be as clear, transparent, and objective as possible, and be based on factors related only to the likelihood and magnitude of benefit from the medical resources and should always minimize inequitable outcomes. Factors that have no bearing on the likelihood or magnitude of benefit, include but are not limited to, race, disability, gender, sexual orientation, gender identity, ethnicity, ability to pay, socioeconomic status, perceived social worth, perceived quality of life, immigration status, incarceration status, homelessness or past or future use of resources. Such factors are not to be used as a basis for clinical decisions.

### **Access to medication**

Anti-SARS-CoV2 mAb, and oral antivirals are available through state-funded mAb infusion sites across the Commonwealth. These state-funded infusion sites include Athol, Everett, Fall River, Holyoke, Lowell, Pittsfield, and Plymouth. **Prior to referring patients, providers are strongly urged to consider the currently constrained supply of these therapeutics and refer those patients at the highest risk of developing severe COVID-19.**

The Gothams referral form for monoclonal antibody and antiviral therapies may be found here: <http://www.gothams.com/referral-form>.

Additionally, hospitals and other healthcare providers throughout Massachusetts serve as sites for the distribution of COVID-19 therapeutics and will administer mAb and remdesivir and dispense oral antiviral therapy as supplies are available. The [COVID-19 Therapeutics Locator](#) can be used to locate sites offering mAb and antiviral therapies. For referrals to hospital infusion sites, providers should use the contact number for the site listed on for the site on the locator map. Patients or their representative should follow the instructions provided by the healthcare provider as to how to receive the dispensed medication at the COVID-19 therapeutics site.

Oral antiviral therapy will also be available through prescription requests and distributed through community health centers (CHC) in areas with a high burden of COVID-19. For patients who are cared for through the CHC, oral antivirals will be prescribed by CHC clinicians and filled through the CHC pharmacy.

As oral antiviral therapies become more available, the number of sites dispensing the medication will increase.