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**Clinical Guidance on Therapeutics for COVID-19**

*Issued December 5, 2022*

 **Executive Summary**

* On 11/30/2022 the U.S. Food and Drug Administration (FDA) announced bebtelovimab is not currently authorized for emergency use because it is not expected to neutralize Omicron subvariants BQ.1 and BQ.1.1, which now constitute the majority of isolates in the U.S.
* Nirmatrelvir/ritonavir (PAXLOVID) is the preferred treatment for most patients with mild-to-moderate COVID-19 at increased risk of progression to severe disease and should be prescribed to patients who qualify, including patients where it is appropriate to hold or adjust certain other medications to safely administer the five-day nirmatrelvir/ritonavir (PAXLOVID) course. It continues to be widely available and in adequate supply in Massachusetts.
* Remdesivir is the most effective alternative therapy for the treatment of COVID-19 when use of nirmatrelvir/ritonavir (PAXLOVID) is not clinically appropriate.
* Tixagevimab/cilgavimab (EVUSHELD) continues to be authorized by the FDA and there is no currently available alternative monoclonal antibody for pre-exposure prophylaxis of COVID-19. However, an increasing proportion of variants are likely NOT to be susceptible to this agent and those who receive it should be cautioned to use additional measures to prevent infection.

The purpose of this document is to provide guidance to health care providers on the use of therapeutics to treat individuals with COVID-19. Therapeutics should be considered for all patients with a positive test for COVID-19 who are symptomatic and at increased risk for moderate-to-severe disease progression. This group includes a large percentage of all MA residents who are eligible due to heart, lung, liver, or kidney disease, diabetes, pregnancy, dementia, cancer, disability, substance use disorder, mental health disorder, age over 50 years, overweight/obesity and immunocompromise.

Full CDC list of eligibility criteria is here: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>.

All individuals who qualify for treatment under the applicable Emergency Use Authorization (EUA) or approval from the Food and Drug Administration (FDA), regardless of vaccination status, are eligible to receive therapeutics for mild-to-moderate COVID-19.

**Providers should ensure that eligible patients have access to and receive these critical and available therapies. Treatments are available widely. Use the** [**COVID-19 Therapeutics Locator**](https://mdphgis.maps.arcgis.com/apps/instant/nearby/index.html?appid=82983fa9f6d44e2aaf1d5bd420aa57ff&sliderDistance=24) **to connect patients to locations near them.**

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

Antiviral medications are currently the only treatments that should be used for individuals with mild-to-moderate COVID-19.

NIRMATRELVIR/RITONAVIR (PAXLOVID)

The oral antiviral therapy [nirmatrelvir co-packaged with ritonavir (PAXLOVID)](https://www.fda.gov/media/155049/download) 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. Nirmatrelvir boosted with ritonavir (nirmatrelvir/r) is expected to retain activity against all known variants of SARS-CoV-2.

Nirmatrelvir/r is the most effective medication currently authorized for the treatment of COVID-19. Clinical trials have shown 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 the FDA EUA, 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-19.1

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. Individuals who are hospitalized for reasons not related to COVID-19 may be treated with nirmatrelvir/r while hospitalized.

The standard dose of nirmatrelvir/r is 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg of ritonavir (one 100 mg tablet), with all three tablets taken twice daily for five days. A single five-day course is dispensed in a blister pack. The nirmatrelvir/r dose is reduced to 150 mg of nirmatrelvir (one 150 mg tablet) with 100 mg of ritonavir (one 100 mg tablet) for moderate renal impairment (eGFR ≥30 to < 60 mL/min), with both tablets taken twice daily for five days. This presentation is available in a dose-reduced blister pack. Nirmatrelvir/r is not recommended in patients with severe renal impairment (eGFR < 30 mL/min) or severe hepatic impairment (Child-Pugh Class C).

Nirmatrelvir/r should be prioritized as treatment for individuals diagnosed with COVID-19 who are within five days of symptom onset and who are at risk for severe COVID-19. While nirmatrelvir/r has significant drug-drug interactions with some medications, primarily due to the ritonavir component, many of these can be managed by holding or substituting medications during treatment. Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient’s concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs and refer to resources such as the [Liverpool COVID-19 Drug Interactions](https://www.covid19-druginteractions.org/) website[[1]](#footnote-2), and the nirmatrelvir/r [EUA Fact Sheet](https://www.fda.gov/media/155050/download) for additional guidance regarding potential drug-drug interactions. Nirmatrelvir/r should be avoided in individuals on medications not compatible with protease inhibitors or that cannot be temporarily held. If, after reviewing for any drug-drug interactions, nirmatrelvir/r cannot be safely prescribed, clinicians should consider the alternate therapeutics remdesivir and molnupiravir.

Rebound of COVID-19 has been observed in a small subset of patients treated with nirmatrelvir/r. Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) were observed in some individuals receiving nirmatrelvir/r and placebo in the initial nirmatrelvir/r investigational trial. Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through day 28 following the single 5-day course of nirmatrelvir/r treatment. Post-treatment viral RNA rebound also was not associated with drug resistance. Case reports suggest that individuals treated with nirmatrelvir/r who have experienced COVID-19 rebound have had mild illness two to eight days after completion of therapy. Some individuals with COVID-19 rebound had negative test results after nirmatrelvir/r treatment and had subsequent positive viral antigen and/or reverse transcriptase polymerase chain reaction (RT-PCR) testing. Individuals with COVID-19 rebound should re-isolate for at least five days and should wear a mask for 10 days after rebound symptoms started.[[2]](#footnote-3)

REMDESIVIR (VEKLURY)

[Remdesivir (VEKLURY)](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) is an FDA-approved antiviral therapy for use in adult and pediatric patients (28 days of age and older and weighing at least 3 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.

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 [package insert](https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) for information on dosing for pediatric patients weighing 3 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3 kg.

Remdesivir decreased the risk of severe COVID-19 by 87% in clinical trials. It is considered the next best therapy in situations where nirmatrelvir/r is not clinically appropriate.

Remdesivir is expected to retain activity against the currently circulating variants.

MOLNUPIRAVIR (LAGEVRIO)

A second oral antiviral therapy, [molnupiravir](https://www.fda.gov/media/155054/download) (LAGEVRIO), 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. This drug is expected to retain activity against all known variants of SARS-CoV-2.

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-19.1
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 years 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.

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.

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

There are no monoclonal antibodies currently authorized for treatment of COVID-19. On November 30, 2022, the FDA announced that [bebtelovimab](https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region) is not currently authorized for emergency use in the U.S. because it is not expected to neutralize the Omicron subvariants BQ.1 and BQ.1.1. FDA previously withdrew authorization for [casirivimab/imdevimab (REGEN-COV)](https://www.fda.gov/media/145611/download), and [bamlanivimab/etesevimab](https://www.fda.gov/media/145802/download) (January 24, 2022), and for [sotrovimab](https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization) (April 5, 2022) when the dominant variant was resistant to those agents.

**Prophylactic therapy for COVID-19**

TIXAGEVIMAB/CILGAVIMAB (EVUSHELD)

The long-acting mAb [tixagevimab/cilgavimab (EVUSHELD](https://www.fda.gov/media/154701/download)) 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, including high dose corticosteroids (≥ 20 mg/day of prednisone or equivalent) and tumor necrosis factor inhibitors, or
3. Individuals for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction.

Tixagevimab/cilgavimab (EVUSHELD) is likely to have limited effectiveness against currently circulating variants. There are, however, no alternative therapies currently available for pre-exposure prophylaxis. Providers should use their clinical judgement for each patient to determine whether it will benefit them and communicate any additional risk-mitigating steps their patients should take given the potential limited effectiveness.

For pre-exposure prophylaxis, the current authorized initial dose of tixagevimab/cilgavimab is 300 mg of tixagevimab and 300 mg of cilgavimab. The medications should be administered as two separate intramuscular injections, ideally in the gluteal or vastus lateralis muscle. A repeat dose of 300 mg of tixagevimab and 300 mg of cilgavimab should be administered every six months. Repeat dosing should be timed from the date of the most recent tixagevimab/cilgavimab dose.

[Casirivimab/imdevimab](https://www.fda.gov/media/145611/download) and [bamlanivimab/etesevimab](https://www.fda.gov/media/145802/download) were previously authorized for use as postexposure prophylaxis. Given resistance of predominant variants in Massachusetts to these medications, their use for post-exposure prophylaxis is not authorized at this time.

**Recommendations**

**Currently, available supply of COVID-19 therapeutics in Massachusetts is not a barrier to eligible patients’ access to treatment.** We strongly urge providers to ensure eligible patients have access to and receive these critical and available therapies.

All symptomatic individuals with mild to moderate COVID-19 who are at increased risk for severe COVID-19 are eligible to receive therapeutics, including nirmatrelvir/r, remdesivir, and molnupiravir. Unvaccinated individuals and vaccinated individuals who are not up to date with COVID-19 vaccination are at higher risk for severe disease. Clinical risk factors include age ≥ 50 years (with risk increasing substantially at age ≥ 65years), cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt of immunosuppressive medications, obesity (body mass index ≥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](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

**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. The decision to treat a patient should be based on an individualized assessment of risks and benefits.**

Nirmatrelvir/r should be prioritized as treatment for individuals diagnosed with COVID-19 who are within five days of symptom onset and who are at risk for severe COVID-19. If nirmatrelvir/r is indicated but not clinically appropriate, remdesivir should be considered. Molnupiravir may be used if all other therapies are not clinically appropriate or feasible.

For patients with COVID-19 who are at risk for severe disease and who are between five and seven days of symptom onset, remdesivir should be considered. There is no drug authorized or approved for treatment of mild to moderate COVID-19 after seven days from symptom onset.

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**

Massachusetts has supply available to meet the needs of all residents who can benefit from these treatments. There are several pathways for residents to access therapy.

Therapeutics may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs. Nirmatrelvir/r may also be prescribed for an individual patient by a state-licensed pharmacist under specific conditions outlined in the [EUA](https://www.fda.gov/media/155050/download). Oral antiviral treatments are widely available via retail pharmacies across the Commonwealth with a prescription from a licensed healthcare provider.

Oral antiviral therapy is also available for individuals aged ≥ 18 year living in Massachusetts through a state-supported [telehealth platform](https://www.mass.gov/info-details/free-telehealth-for-covid-19-treatment-with-paxlovid). Using the [telehealth platform](https://www.mass.gov/info-details/free-telehealth-for-covid-19-treatment-with-paxlovid), individuals with COVID-19 will be assessed by a licensed provider to ensure that they meet clinical criteria for treatment. If eligible, medications will be prescribed through the telehealth platform will be delivered to the patient at their home address or prescriptions can be filled through retail pharmacies.

A subset of these retail pharmacies also provides “test-to-treat” service, with rapid testing followed by medical evaluation, prescribing and dispensing of medications all on-site. The [COVID-19 Therapeutics Locator](https://mdphgis.maps.arcgis.com/apps/instant/nearby/index.html?appid=82983fa9f6d44e2aaf1d5bd420aa57ff&sliderDistance=24) can be used to locate retail pharmacies offering oral antiviral therapies, including those pharmacies with test-to-treat capability.

Oral antiviral therapy is also 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.

Hospitals and other healthcare providers throughout Massachusetts serve as sites for the distribution of COVID-19 therapeutics and will administer remdesivir and dispense oral antiviral therapy as supplies are available.

Additionally, remdesivir antiviral therapy is available through [state-funded therapeutics access sites](https://www.mass.gov/info-details/information-for-providers-about-therapeutic-treatments-for-covid-19#access-) across the Commonwealth. Remdesivir infusions can also be accessed through state-supported home infusion service

1. [Liverpool COVID-19 Interactions (covid19-druginteractions.org)](https://www.covid19-druginteractions.org/checker) [↑](#footnote-ref-2)
2. <https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf> [↑](#footnote-ref-3)