The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

CHARLES D. BAKER
Governor

KARYN E. POLITO
Lieutenant Governor

MARYLOU SUDDERS
Secretary

MARGRET R. COOKE
Commissioner

Tel: 617-624-6000
www.mass.gov/dph

# Clinical Guidance on Therapeutics for COVID-19

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**Executive Summary**

- Nirmatrelvir/ritonavir (PAXLOVID) is the preferred treatment for most patients with mild-to-moderate COVID-19 at high risk of progression to severe disease and continues to be widely available and in adequate supply in Massachusetts
- The dose pack presentation of nirmatrelvir/ritonavir (PAXLOVID) for individuals with moderate renal impairment has been updated.

The purpose of this document is to provide guidance to health care providers on the use of therapeutics to treat COVID-19 positive individuals, as well as pre-exposure prophylaxis for immunocompromised individuals. Therapeutics should be considered for all patients with a positive test for COVID-19 who are symptomatic and at risk for moderate-to-severe disease progression. This group includes over 40 percent 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 65, overweight/obesity and immunocompromised.

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

At present, there are two general classes of treatment for mild-to-moderate COVID-19: antivirals and monoclonal antibodies (mAb). Presently 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 must ensure that eligible patients have access to and receive these critical and available therapies. Treatments are available widely. Use the COVID-19 Therapeutics Locator to connect patients to locations near them.**

## 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). This drug is expected to retain activity against all known variants of SARS-CoV-2.

*Revised 4/26/2022*: Providers should ensure that they are reading the most current version of this guidance as recommendations frequently change. Find the latest document at: https://www.mass.gov/info-details/information-for-providers-about-therapeutic-treatments-for-covid-19#guidance-

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.[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.

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 avoided in individuals on medications not compatible with protease inhibitors or that cannot be temporarily held.

A second oral antiviral therapy, molnupiravir (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.

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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 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 decreased the risk of severe COVID-19 by 87% in clinical trials.

Remdesivir is expected to retain activity against the Omicron variant, including the BA.2 subvariant.

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

Bebtelovimab is the only anti-SARS-CoV-2 monoclonal antibody therapy currently authorized for treatment of COVID-19 pursuant to Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA).

Bebtelovimab is authorized 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. Individuals who have received a positive COVID-19 test (antigen or molecular)
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 ≥ 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$^{th}$ percentile for age/gender), other medical conditions that place one at high risk for severe disease[1]
4. Bebtelovimab is authorized in individuals for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate

**In general, treatments for COVID-19 should be started as soon as possible after diagnosis of COVID-19**. Bebtelovimab is authorized for treatment within the first seven days of COVID-19 symptom onset.

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, monoclonal antibody 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 monoclonal antibody therapy should not receive additional monoclonal antibody doses.

Monoclonal antibody therapy decreases the risk of severe disease from COVID-19 between 70% and 85% in clinical trials. SARS-COV-2 variants, however, may be resistant to certain monoclonal antibodies, limiting treatment efficacy of those agents.

On January 24, 2022, the FDA withdrew authorization for monoclonal antibodies casirivimab/imdevimab (REGEN-COV), and bamlanivimab/etesevimab as treatment for COVID-19 because because the dominant Omicron variant is resistant to these agents. Additionally, given that sotrovimab has reduced effectiveness against SARS-CoV2 Omicron subvariant BA.2, the FDA revised the EUA on April 5, 2022 withdrawing authorization for treatment of COVID-19 when this subvariant is the dominant virus. as is the case in the United States currently. Monoclonal antibody therapies casirivimab/imdevimab, balmanivimab/etesevimab and sotrovimab may be authorized for use in the future should the prevalence of the Omicron variant decrease.

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

Bebtelovimab shows high activity against all known variants (including BA.2) in laboratory studies but only limited clinical data on effectiveness. As a result, bebtelovimab should be used as the monoclonal antibody of choice in regions where BA.2 is the dominant subvariant if preferred therapies are not feasible or appropriate to use.

For treatment of mild to moderate COVID-19, the authorized dose of bebtelovimab is 175 mg administered as a single intravenous injection over at least 30 seconds. The authorized dose of sotrovimab is 500 mg, administered as a single intravenous infusion over 15 minutes if diluted in a 50 ml infusion bag or 30 minutes if diluted in a 100 ml bag.

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

**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, 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 confers protection against the Omicron variant and should be used in an environment when Omicron variant is dominant. Based on the most recent data available, however, tixagevimab/cilgavimab may be less active against certain Omicron subvariants. On February 25, 2022, the FDA increased the recommended initial dose of tixagevimab/cilgavimab. The dosing regimen was revised because available data indicate that a higher dose may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 compared to the originally authorized dose.

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.

Individuals who received the prior initial dose of 150 mg of tixagevimab and 150 mg of cilgavimab should receive an additional dose of tixagevimab/cilgavimab as soon as possible. For individuals who

received their initial dose less than three months ago, that individual should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab. For individuals who received their initial dose more than three months ago, the individual should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab.

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 and bebtelovimab are not authorized for post-exposure prophylaxis.

**Recommendations**

**Currently, available supply of COVID-19 therapeutics in Massachusetts is not a barrier to eligible patients' access to treatment.**

All symptomatic individuals with mild to moderate COVID-19 who are at risk for severe COVID-19 are eligible to receive therapeutics, including nirmatrelvir/r, remdesivir, bebtelovimab (if BA.2 is the predominant variant in the region), and molnupiravir, regardless of their National Institutes of Health COVID-19 risk tiers or vaccination status. We strongly urge providers to ensure eligible patients have access to and receive these critical and available therapies, regardless of vaccination status or risk tier. The tiers provided below are only applicable should there be insufficient supply of these federally allocated therapeutics to fulfill patient need for treatment.

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. In the setting while the Omicron subvariant BA.2 is dominant, if nirmatrelvir/r is indicated but not appropriate or available, remdesivir should be considered. Bebtelovimab may be used if nirmatrelvir/r, and remdesivir are not clinically appropriate or unavailable. Molnupiravir may be used if all other therapies are not available.

**Table: Treatment recommendations for mild to moderate COVID-19 while the Omicron subvariant BA.2 is dominant**

The NIH COVID-19 risk tiers provided below are only applicable when there is insufficient supply. As of 2/18/2022, there are no supply constraints.

| NIH Tier | Patient characteristics* | | Recommendation *Based on symptom onset timeline* | |
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| | | | **Within 5 days of symptom onset** | **Between 5 – 7 days of symptom onset** |
| 1 | Moderate-to-severe immunosuppression; Not fully vaccinated and age ≥ 75 years; Not fully vaccinated and age ≥ 65 years plus additional risk factor | *Patients from all tiers* | Nirmatrelvir/r preferred.<br><br>If nirmatrelvir/r, not appropriate or available, remdesivir preferred.<br><br>If nirmatrelvir/r or remdesivir not appropriate or available, bebtelovimab preferred.<br><br>Molnupiravir may be used if other therapies not appropriate or available. *** | Remdesivir preferred.<br><br>If remdesivir not appropriate or available, bebtelovimab may be used. |
| 2 | Not fully vaccinated and age ≥ 65; Not fully vaccinated and age < 65 plus additional risk factor | | | |
| 3 | Vaccinated** and age ≥ 75; Vaccinated and age ≥ 65 years plus additional risk factor | | | |
| 4 | Vaccinated and age ≥ 65 years; Vaccinated and age < 65 plus additional risk factor | | | |
| N/A | Any adult (or pediatric patient over age 12 and >40 kg) at increased risk of severe COVID-19 | | | |

National Institutes of Health (NIH)

*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 ≥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. Therapeutics for COVID-19 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 monoclonal antibodies or antivirals for a patient should be based on an individualized assessment of risks and benefits. Use of monoclonal antibodies 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.

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

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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 monoclonal antibody 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**

Massachusetts has supply available to meet the needs of all residents who can benefit from these treatments.

Oral antiviral treatments are widely available via retail pharmacies across the Commonwealth with a prescription from a licensed healthcare provider. 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 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.

Anti-SARS-CoV2 monoclonal antibodies, and antivirals are available through state-funded Gothams therapeutics access sites across the Commonwealth.

The Gothams referral form for monoclonal antibody and antiviral therapies may be found here: http://www.gothams.com/referral-form. Individuals with COVID-19 are also able to access medications through Gothams sites directly by calling the self-referral telephone number (508) 213-1380.

Additionally, hospitals and other healthcare providers throughout Massachusetts serve as sites for the distribution of COVID-19 therapeutics and will administer monoclonal antibodies and remdesivir and dispense oral antiviral therapy as supplies are available. The COVID-19 Therapeutics Locator can be used to locate sites offering monoclonal antibodies 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.

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Tixagevimab/cilgavimab (EVUSHELD) is available through many academic and some regional medical centers, state-sponsored infusion sites, as well as some individual providers serving at-risk individuals. Providers should contact academic centers with whom they have affiliations or Gothams sites for their patients seeking pre-exposure prophylaxis with tixagevimab/cilgavimab.

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