Beth Israel Lahey Health

Last Update March 30th 2022

The purpose of this guideline is to outline the criteria for use of COVID-19 monoclonal antibodies and fulfill the regulatory requirements of the Emergency Use Authorization (EUA) for these drugs. This guideline will not cover all potential clinical scenarios and clinical judgement is required for optimal application.

COVID-19 Monoclonal Antibody (mAb) Guidelines

Medication	Bebtelovimab	Tixagevimab & Cilgavimab (Evusheld)
Indications	Treatment Mild-Moderate COVID-19	Pre-exposure prophylaxis (PrEP)

Overview

Omicron Variant Update:

- Omicron BA.2 is predominant our region. Due to reduced activity against this subvariant **FDA has withdrawn the EUA for sotrovimab in Massachusetts**.
- Bebtelovimab is active against Omicron including BA1.1 and BA.2, and was given EUA to treat mild-moderate COVID-19 in high-risk patients treated within 7 days of symptom onset if other treatments are not available or appropriate.
- Tixagevimab & cilgavimab (Evusheld) is indicated for pre-exposure prophylaxis (PrEP) for moderate-severely immunocompromised patients only. Given reduced activity of this combination against Omicron BA.1.1, a dose increase was implemented for new patients and previously treated patients have been asked to return for a "catch-up" dose.
- There are no mAbs active against Omicron that are currently authorized for post-exposure prophylaxis.
- Bamlanivimab & etesevimab and casirivimab & imdevimab lack of efficacy against Omicron variants and are not currently authorized for use.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the use of these monoclonal antibody products for the following indications:

- **Treatment** of mild-moderate symptomatic COVID-19:
  - Outpatients at high risk for progressing to severe COVID-19 and hospitalization
    - Risk factors for progression to severe COVID-19
    - Prioritization criteria are outlined by the Drug Shortage Task Force in the setting of shortage
  - Symptomatic patients who are hospitalized for a reason other than COVID-19 infection and at high risk for progressing to severe COVID-19

- **Pre-exposure prophylaxis**
  - Tixagevimab & cilgavimab (Evusheld)

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BILH CRITERIA FOR USE OF MONOCLONAL ANTIBODY THERAPY

Criteria for TREATMENT of symptomatic COVID-19:

Must meet ALL inclusion criteria:

1. Have one or more mild-moderate COVID-19 symptoms, with an onset **no greater than 7 days prior** to the date the medication is administered. Symptoms may include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath with exertion, loss of taste/smell.
2. **Must have a PCR or antigen test confirming SARS-CoV-2 infection** from a specimen obtained preferably no greater than 7 days prior to the date the medication is administered.
3. Have at least one risk factor for progression to severe COVID-19
4. Age ≥ 18 (Pediatric COVID-19 mAb therapy is not currently available at BILH)
5. The patient or legally authorized representative gives verbal consent and/or assent

Must not meet ANY exclusion criteria:

1. Hospitalization for the treatment of COVID-19 at any point during the present course of illness
2. Oxygen saturation (SpO2) ≤ 93% on room air due to COVID-19 in those not on chronic oxygen therapy
3. An increase in baseline oxygen flow rate due to COVID-19 in those who are on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
4. Allergies to any of the constituent products in the antibody combination
5. Any acute clinical instability including hemodynamic instability, ventilatory or vasopressor support

Criteria for PRE-EXPOSURE PROPHYLAXIS:

Must meet ALL criteria:

1. No symptoms of COVID-19
2. No confirmed exposure to COVID-19 within the past 5 days
3. Meet **one** of the following criteria:
    a. Have a moderate-severely immunocompromising health condition in which they may not mount an adequate immune response to COVID-19 vaccination
    b. Have a history of severe adverse reactions to a COVID-19 vaccine and/or component(s) of those vaccines, therefore vaccination with an available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended (e.g. history of myocarditis after prior COVID-19 vaccine administration or severe hypersensitivity reaction AND contraindication to other available COVID-19 vaccine

Other considerations

Vaccination Status:

- Completion of a COVID-19 vaccine series (including a third dose of mRNA vaccine in the appropriate population and booster) is **STRONGLY** recommended.
- For individuals who have received a COVID-19 vaccine, tixagevimab & cilgavimab should be administered at least two weeks after vaccination.
- Tixagevimab & cilgavimab is **NOT** a replacement for COVID-19 vaccine and vaccination should not be delayed for this therapy.

Prior CoVID-19 infection

- No data are currently available regarding use of tixagevimab & cilgavimab in individuals with prior COVID-19 infection. Use of pre-exposure prophylaxis should be deferred until after the patient is no longer under isolation for COVID-19. If monoclonal antibody has been given for the treatment of COVID-19, and use of sotrovimab or bebtelovimab can be confirmed, it may be reasonable to wait 30 days prior to consideration of pre-exposure prophylaxis.

Risk Factors for Progression to Severe COVID-19
Age ≥65 years
Autoimmune disease requiring ongoing systemic therapy
Cardiovascular disease or hypertension
Chronic kidney disease
Chronic liver disease
Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
Diabetes
High Risk Body-Mass Index (BMI): • 25-30 kg/m^2 AND not fully vaccinated with primary 1-2 dose series (no vaccination or series completed less than 2 weeks prior) • >30 kg/m^2 regardless of vaccination status
Immunocompromising health conditions categorized as mild, moderate, or severe (see BILH definitions)
Medical-related technological dependence (e.g. tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])
Neurodevelopmental disorders (e.g. cerebral palsy, genetic/metabolic syndromes, severe congenital anomalies)
Pregnancy and up to 6 weeks post-partum
Race/ethnicity that is associated with a higher risk of hospitalization or death from COVID-19, including Black or African American, Hispanic or Latinx, American Indian or Alaska Native
Sickle cell disease or other hemoglobinopathy

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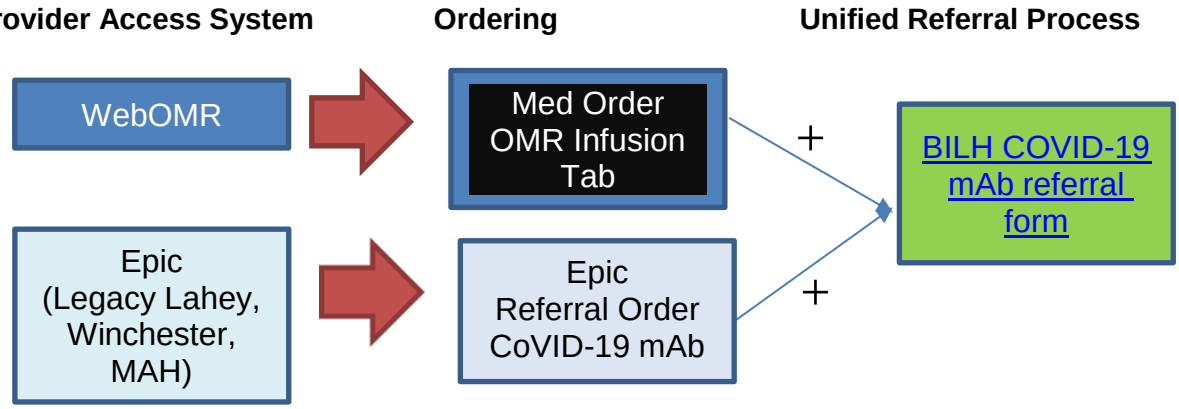
Outpatient Ordering and Referral Process for COVID-19 mAb TREATMENT of Mild-Moderate Infection:



Referrals are reviewed by the centralized prioritization team each morning, Monday-Friday. Referrals will not be reviewed weekends or holidays. In the instance of drug shortages or other constrained resources, prioritization for treatment is based on BILH Drug Shortage Task Force guidance.

If a patient is assigned a treatment slot at either the BIDMC or LHMC site, the patient will be contacted directly to be scheduled for therapy. If there are no treatment slots available, the referring provider will be notified.

NOTE: Due to the logistics of a 3 day course of remdesivir and lack of weekend staffing, bebtelovimab may be prioritized for patients presenting some days.

Attempts will be made to serve patients at the closest geographic site, but this cannot be guaranteed. If you have any questions, you may email: covidmab@bidmc.harvard.edu

Inpatient Ordering Instructions for TREATMENT:

- Monoclonal antibody therapy is limited to ordering for patients with mild-moderate COVID-19 who are hospitalized for reasons unrelated to COVID-19. Antibody therapy may increase the risk of worse outcomes in patients with severe COVID-19 requiring hospitalization.
- The ordering provider must complete the following steps:
    1. Write a note in the applicable EHR documenting that the patient meets eligibility criteria and understands the risks and benefits of treatment under the EUA.
        - BIDMC Providers: Use the appropriate macro located in the COVID-19 Monoclonal Antibody folder:
            - COVID-19 mAb (symptomatic inpatient)
    2. Place an order for bebtelovimab in the applicable EHR.
        - BIDMC Providers: Obtain approval from Antimicrobial Stewardship (AST pager 39244). The medication will only be approved for use 8 am to 6 pm.

COVID-19 mAb for Pre-exposure Prophylaxis

- BILH is engaged in identification and outreach to patients with moderate-severe immunosuppression to offer treatment with tixagevimab & cilgavimab.
- A Sharepoint referral form is currently under construction.

Pregnancy and Breast Feeding

There is limited experience treating pregnant women or breastfeeding mothers with these antibodies. The benefit of receiving monoclonal antibody therapy may be greater than the risk from the treatment, but this should be discussed with relevant experts on a case-by-case basis.

COVID-19 Vaccination

Monoclonal antibody therapy for mild-moderate COVID may be given to patients who have previously received the COVID-19 vaccine and conversely vaccination should not be delayed after administration of a monoclonal antibody.

Dosing and Route of Administration

For treatment of symptomatic COVID-19:

Bebtelovimab
175 mg IV once

For prophylaxis following exposure (PEP) to SARS-CoV-2:

No EUA for any mAb for this indication at the present time

For pre-exposure prophylaxis (PrEP) to SARS CoV-2:

Tixagevimab & Cilgavimab (Evusheld) NEW DOSING
TIXAgevimab **300** mg, CILgavimab **300** mg IM (2 separate injections) once*

*For patients who have already received a single dose of TIXAgevimab 150 mg, CILgavimab 150 mg, a **"catch-up" dose** of an additional TIXAgevimab 150 mg, CILgavimab 150 mg should be administered

- Redosing may be warranted in the future, but evidence is lacking and no recommendation can be made at present.

Significant Drug-Drug Interactions

Monoclonal Antibodies are **not** metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. These are also **not** renally eliminated.

Adverse reactions

	Bebtelovimab	**Tixagevimab & Cilgavimab (Evusheld)**
Infusion related reactions	Similar rates to placebo (0.3%)	Not applicable, site reactions near IM injection
Hypersensitivity reactions	Rash mild to moderate at 0.8%, comparable to placebo.	Not noted during trials.
Injection site reactions	N/A	Use with caution as with any IM injection in patients with severe thrombocytopenia or a coagulation disorder.
MACE: Major Adverse Cardiac Events	Not observed	Clinical trial: A higher rate of cardiac events including MI and heart failure (0.2-0.6%) were observed versus placebo (0.1-0.2%).

	Bebtelovimab	Tixagevimab & Cilgavimab (Evusheld)
General:	Nausea (0.8%), Vomiting (0.7%)	Headache and fatigue rates similar to placebo, 4-6%.

Under the EUA, FDA is requiring health care providers who prescribe this combination to report all medication errors and serious adverse events considered to be potentially related to this combination through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178.

FDA MedWatch forms should be provided to the corresponding drug company:

	Tixagevimab & Cilgavimab (Evusheld)	Bebtelovimab
Company	Aztra Zeneca Pharmaceuticals	Lilly
Fax	1-866-742-7984	1-317-277-0853
Email	contactazmedical.astrazeneca.com	mailindata_gsmtindy@lilly.com
Phone	1-800-236-9933	1-855-545-5921

Requirements for the EUA by Discipline

Prescribers

1. Review the *EUA Fact Sheet for Providers* and the *inclusion/exclusion criteria* above

	Tixagevimab & Cilgavimab (Evusheld)	Bebtelovimab
EUA Detailed Fact Sheets	Fact Sheet for Health Care Providers	Fact Sheet for Health Care Providers
Frequently Asked Questions (FAQ) for EUA	FAQ on EUA for Evusheld	FAQ on EUA on Bebtelovimab

2. *Review the EUA Fact Sheet for Patients/Caregivers* with the patient or legally authorized representative. An interpreter is recommended to assist if the patient speaks another language.

	Tixagevimab & Cilgavimab (Evusheld)	Bebtelovimab
English Language	FDA Patient/Caregiver Fact Sheet	FDA Patient/Caregiver Fact Sheet
Spanish Language	Spanish language Fact Sheet not yet available	Spanish language Fact Sheet

3. Document in the medical record that the patient/health care proxy understands and accepts the risks of the investigational treatment
4. Report medication errors or serious adverse events; see section above.

Pharmacists

Review Fact Sheets as necessary (provided above)

Dispensing & inventory information

- Given the unique qualities of this EUA, inventory will be maintained on count.

- The lot number and an appropriate quantity of drug must be logged for each patient with daily sign-out if lot numbers vary

Intravenous Preparation Instructions

Bebtelovimab
• Materials for preparation ○ **One** bebtelovimab 175 mg/2 mL (87.5 mg/mL) ○ One syringe 2 – 3 mL ○ One polycarbonate and polyvinylchloride without di-ethylhexylphthalate (DEHP) syringe extension set ○ Remove bebtelovimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake vial. Inspect the vial. ○ Withdraw 2 mL from the vial into the syringe. ○ Discard any product remaining in the vial. ○ Label with beyond use date/time

For "catch-up" dose of tixagevimab (150 mg) & cilgavimab (150 mg) - for patient who previously received tixagevimab (150 mg) and cilgavimab (150 mg) prior to February 28 2022

Intramuscular Preparation Instructions FOR tixagevimab & cilgavimab (Evusheld) ONLY

1. Remove the separate **tixagevimab (150 mg/1.5 mL) and cilgavimab (150 mg/1.5 mL)** vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.
2. Inspect vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to slightly yellow.
3. Withdraw 1.5 mL of tixagevimab solution and 1.5 mL of cilgavimab solution into TWO separate syringes. Discard unused portion in vials.

For patients prescribed tixagevimab & cilgavimab (Evusheld) after February 28 2022

Intramuscular Preparation Instructions FOR tixagevimab (300 mg) & cilgavimab (300 mg) ONLY - NEW 2/22

1. Remove **TWO** of each separate **tixagevimab (150 mg/1.5 mL) and cilgavimab (150 mg/1.5 mL)** vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.
2. Inspect vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution should be clear to slightly opalescent, colorless to slightly yellow.
3. Withdraw **3** mL of tixagevimab solution and **3** mL of cilgavimab solution into TWO separate syringes. Discard unused portion in vials.

Storage

- **Tixagevimab & Cilgavimab (Evusheld)**

- Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light. The solution in each vial is preservative-free.
- Once the solution is drawn up into a syringe, it loses potency and must be administered before 4 hours.

- **Bebtelovimab**
  - Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Nursing

Review Fact Sheets as necessary (provided above)

Intravenous infusion instructions are the same for all three products:

	Bebtelovimab
Infusion sets and filters	polycarbonate and polyvinylchloride without di-ethylhexylphthalate (DEHP) syringe extension set
Infusion NS only	Slow (30 seconds) injection to extension set
Compatibility	Administer only with NS. NO concomitant medications
Flushing	Flush tubing with NS to ensure complete delivery
Monitoring	Monitor for infusion reactions or hypersensitivity for at least **60 minutes** after.

Intramuscular Administration Instructions (FOR Tixagevimab & Cilgavimab (Evusheld) ONLY)

- Administer the two components of EVUSHELD consecutively.
  - Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
  - Clinically monitor individuals after injections and observe for at least 1 hour
    - Given the new higher volume, injection site pain and discomfort has been reported more commonly. Use of ice packs and/or post administrative ibuprofen or acetaminophen may help to alleviate this pain.

General Drug Related Warnings

Infusion/administration related reactions

- Potential based on observational data: hypotension, nausea, vomiting, diaphoresis, shivering

If signs/symptoms occur, evaluate the severity and consider holding the infusion or future infusions/injections based on severity

Essential medications to be kept in the infusion/administration unit:

- Albuterol inhaler
- Diphenhydramine 50 mg injection
- Epinephrine 0.1 mg/mL (1 mg/10mL) OR epinephrine auto-injector 0.3 mg
- Methylprednisolone 100 mg injection

Major studies informing the EUAs

	Tixagevimab & Cilgavimab (Evusheld)	Bebtelovimab
Study	Unpublished PROVENT trial	Unpublished BLAZE-4
Design	Phase 3, RCT placebo-controlled	Phase 2, RCT, placebo controlled for low risk patients Open label phase 2 for high risk patients
Population	N=5,197 Unvaccinated Outpatients COVID negative with risk factors for advanced disease	Outpatient **Low risk N=381** Randomized to Bam-Etes+Bebtel (n=127) Bebtel alone (n=125) Placebo (n=128) **High risk N=150 NO PLACEBO** Randomized to Bam-Etes+Bebtel (n=50) Bebtel alone (n=100)
Primary Endpoint	Any SARS-CoV-2 RT-PCR positive symptomatic disease occurring post dose prior to day 183	**Low risk** Viral load reduction **High risk** Combined: 29d Rate of hospitalization or all cause mortality
Outcome	Symptomatic COVID-19 cases reduced by 77% (95% confidence interval (CI): 46, 90), compared to placebo	**Low risk** Viral load reduction, day 5 13% vs 21% placebo had persistently high viral load (p=0.098) **High risk** Combined: 29d Rate of hospitalization or all cause mortality 4% combo vs 3% monotherapy
Secondary Endpoints	Percentage of participants that have a post treatment antibody response	**Low risk** Combined: 29d Rate of hospitalization or all cause mortality
Outcome	Not yet available	**Low risk** (2.4%) in combo vs 1.6% w/bebtel alone and 1.6% with placebo

Pharmacology

Each agent binds a unique section of the receptor-binding domain of the spike protein, blocking spike protein attachment to the human ACE2 receptor, fusion, entry and replication. Binding is specific to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2. During the clinical trials,variant identification was not performed, and their presence is potentially underrepresented. Given the increased prevalence of variants and sublineages, the relative activity of these products *in vitro* follow with the caveat that not all variants carry significant mutations and the clinical correlation has not been systematically evaluated.

Relative activity in vitro to Variants

	Sotrovimab	**Tixagevimab & Cilgavimab (Evusheld)**	**Bebtelovimab**
Alpha (B.1.1.7)	Fully active	Fully active	Fully active
Beta (B.1.351)	Fully active	Fully active	Fully active
Gamma (P.1)	Fully active	Fully active	Fully active
Delta (B.1.617.2)	Fully active	Fully active	Fully active
Epsilon (B.1.427/B.1.429)	Fully active	Fully active	Fully active
Iota (B.1.526)	Fully active	Fully active	Fully active
Kappa/no designation (B.1.617.1/B.1.617.3)	Fully active	Fully active	Fully active
Lambda (C.37)	Fully active	Fully active	Fully active
Mu (B.1.621)	N/A	Less active	Less active
Omicron (B.1.1.529)*	Fully active	Active	Active
Omicron (BA.1.1)	Active	Less active	Active
Omicron (BA.2)	Less active	Active	Active

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