COVID-19 Monoclonal Antibody EUA (Emergency Use Authorization) Guidelines

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

| Investigational acronyms | Bamlanivimab & Etesevimab (LY-CoV555, LY3819253) & Etesevimab (LY-CoV016, LY3832479) | Casirivimab & Imdevimab (REGN10933) & Imdevimab (REGN10987) | Sotrovimab (GSK/Vir) |

Overview

- 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 in certain individuals:
    - Outpatients at high risk for progressing to severe COVID-19 and hospitalization
    - Patients who are hospitalized for a reason other than COVID-19 infection and at high risk for progressing to severe COVID-19
  - **Post-exposure prophylaxis (casirivimab-imdevimab and bamlanivimab-etesevimab)**
    - Asymptomatic patients who are at high risk for progressing to severe COVID-19 and hospitalization AND are either unvaccinated or are not expected to mount an adequate immune response to SARS-CoV-2 vaccination.
    - Due to capacity and supply limitations, outpatient post-exposure prophylaxis is not currently available at BILH sites.
  - These products are not approved for patients who are hospitalized due to symptoms of COVID-19 or who require supplemental oxygen due to COVID-19
  - Due to capacity constraints, symptomatic patients with the highest risk of developing severe COVID-19 will be prioritized for treatment, such as those who are unvaccinated and/or immunosuppressed. Prioritization will be based on guidance from a Drug Shortage Task Force.

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Inclusion Criteria for TREATMENT of symptomatic COVID-19

Must meet ALL criteria:

1. Are not hospitalized OR are hospitalized for a reason other than COVID-19 infection
2. Have one or more mild-moderate COVID-19 symptoms, with an onset no more than 10 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.
3. Must have a PCR or antigen test confirming SARS-CoV-2 infection from a specimen obtained no more than 10 days prior to the date the medication is administered.
4. Age ≥ 18 years OR age 12-17 years with weight ≥ 40 kg
5. The patient or legally authorized representative gives verbal consent and/or assent
6. Have at least one risk factor for progression to severe COVID-19
   a. Age ≥65 years
   b. BMI 25-30 kg/m² AND not fully vaccinated with 1-2 dose series (no vaccination or series completed less than 2 weeks prior)
   c. BMI >30 kg/m² regardless of vaccination status
   d. If age 12-17, BMI ≥85th percentile for age/gender (CDC growth charts)
   e. Pregnancy and up to 6 weeks post-partum
   f. Chronic kidney disease
   g. Diabetes
   h. Immunosuppressive conditions:
      i. Autoimmune disease requiring ongoing systemic therapy
      ii. HIV with any CD4 count
      iii. Asplenia or functional asplenia
      iv. Chronic liver disease
      v. Malignancy and primary immunodeficiency as defined on page 4
   i. Immunosuppressive medications as defined on page 4
   j. Cardiovascular disease or hypertension
   k. Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
   l. Sickle cell disease or other hemoglobinopathy
   m. Neurodevelopmental disorders (for example, cerebral palsy), genetic/metabolic syndromes and severe congenital anomalies
   n. Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19))
   o. 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

Exclusion Criteria for TREATMENT of symptomatic COVID-19

Must not meet ANY criteria:

1. Oxygen saturation (SpO2) ≤ 93% on room air due to COVID-19 in those not on chronic oxygen therapy
2. 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
3. Respiratory rate ≥ 30 per minute or Heart rate ≥ 125 per minute
4. Mechanical ventilation or anticipated impending need
5. Allergies to any of the constituent products in the antibody combination
6. Hemodynamic instability requiring use of vasopressors
7. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the clinician could constitute a risk when taking a monoclonal Ab
8. Co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
Inclusion Criteria for PROPHYLAXIS following SARS-CoV-2 exposure
(casirivimab-imdevimab and bamlanivimab-etesevimab)

Due to capacity/supply limitations, outpatient post-exposure prophylaxis is not currently available at BILH sites. Inpatient post-exposure prophylaxis may be available for select patients.

Must meet ALL criteria:

2. Exposure to someone with COVID-19 no more than 4 days prior to the date the medication is ordered. Exposure requires contact with a person with laboratory confirmed COVID-19 who is presumed to be infectious at the time of contact (in the period from 2 days before symptom onset until they meet criteria for discontinuing home isolation). In non-healthcare settings, an exposure can occur irrespective of whether the person with COVID-19 or the contact was wearing a mask or other personal protective equipment (PPE). Exposures include the following scenarios:
   a. being within 6 feet for a total of 15 minutes or more
   b. providing care at home to someone who is sick
   c. having direct physical contact with the person (e.g., hugging or kissing)
   d. sharing eating or drinking utensils
   e. exposure to respiratory droplets from an infected person (from coughing or sneezing)
   f. SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons)
3. A SARS-CoV-2 test (PCR or antigen) obtained within the 2 days prior to medication administration is recommended, as it may be needed for infection control purposes. The result may be negative or positive.
4. Not fully vaccinated with 1-2 dose series (no vaccination or vaccine series completed less than 2 weeks prior) OR an immunocompromising health condition that is listed on page 4
5. Age ≥ 18 years OR age 12-17 years with weight ≥ 40 kg
6. The patient or legally authorized representative gives verbal consent and/or assent
7. Have at least one risk factor for progression to severe COVID-19
   a. Age ≥65 years
   b. BMI >25 kg/m², or if age 12-17 with BMI ≥85th percentile for age/gender (CDC growth charts)
   c. Pregnancy and up to 6 weeks post-partum
   d. Chronic kidney disease
   e. Diabetes
   p. Immunosuppressive conditions:
      vi. Autoimmune disease requiring ongoing systemic therapy
      vii. HIV with any CD4 count
      viii. Asplenia or functional asplenia
      ix. Chronic liver disease
      x. Malignancy and primary immunodeficiency as defined on page 4
   q. Immunosuppressive medications as defined on page 4
   f. Cardiovascular disease or hypertension
   g. Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
   h. Sickle cell disease
   i. Neurodevelopmental disorders (for example, cerebral palsy), genetic/metabolic syndromes and severe congenital anomalies
   j. Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19))
   k. 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
### Immunocompromising Health Conditions

**Active treatment for solid tumor and hematologic malignancies**
Defined as any of the following:
- Last treatment within 3 months
- Remission of malignancy has not been achieved
- Receipt of an immunotherapy such as a checkpoint inhibitor within the last year

<table>
<thead>
<tr>
<th>Receipt of solid organ transplant and taking immunosuppressive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of CAR-T cell or hematopoietic stem cell transplant (within 2 years of transplant or taking immunosuppressive therapy)</td>
</tr>
<tr>
<td>Moderate or severe primary immunodeficiencies (e.g. DiGeorge syndrome, Wiskott-Aldrich, Common Variable Immunodeficiency or hypogammaglobulinemia requiring immunoglobulin therapy)</td>
</tr>
<tr>
<td>Advanced (CD4&lt;200 or presence of AIDS-defining illness) or untreated HIV infection</td>
</tr>
</tbody>
</table>

**Active systemic treatment with any of the following:**
- Chronic daily corticosteroid use (≥10mg prednisone or equivalent daily)
- Alkylating agents (e.g., cyclophosphamide)
- Antimetabolites (e.g., azathioprine, methotrexate)
- Transplant-related immunosuppressive drugs (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate)
- Cancer chemotherapeutic agents classified as severely immunosuppressive
- Tumor-necrosis (TNF) blockers (e.g. etanercept, adalimumab, infliximab)
- B-cell depleting agents (e.g. rituximab)
- Other biologic agents or small molecule inhibitors that are immunosuppressive or immunomodulatory (e.g., IL-1 antagonist, PD-L1, VEGF, EGFR, IL-6, JAK kinase inhibitor)

**Per determination by clinical team based on level of immunocompromise at the time of completion of the primary 2-dose series (i.e., was receiving immunosuppressive therapy during receipt primary series which has now completed):**

<table>
<thead>
<tr>
<th>End-stage renal disease necessitating hemodialysis</th>
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<tbody>
<tr>
<td>Asplenia or functional asplenia</td>
</tr>
</tbody>
</table>
Outpatient Referral Process

- Providers with ordering privileges in WebOMR:
  - Complete a medication order for COVID-19 mAb therapy in the WebOMR infusion tab
  - Complete the BILH COVID-19 mAb referral form
- Providers with ordering privileges in Epic through the legacy Lahey sites:
  - Complete a referral order for COVID-19 mAb therapy in Epic
  - Complete the BILH COVID-19 mAb referral form
- All other BILH providers:
  - Ensure the patient has a BIDMC medical record number. If they do not, please have them call registration at (617) 754-8240
  - Complete the BILH COVID-19 mAb referral form

Referrals are reviewed by the centralized prioritization team each morning, Monday-Friday. Referrals will not be reviewed weekends or holidays. Unvaccinated patients and immunosuppressed patients will be prioritized for treatment.

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.

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 BIDMC

- Monoclonal antibody therapy is limited to ordering for patients 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 webOMR documenting that the patient meets eligibility criteria, and understands the risks and benefits of treatment under the EUA. Use the appropriate macro located in the COVID-19 Monoclonal Antibody folder:
     - COVID-19 mAb (symptomatic inpatient) : For the treatment of qualifying inpatients with mild to moderate symptoms of COVID-19
     - COVID-19 mAb (inpatient post-exposure prophylaxis): For the prevention of symptomatic COVID-19 in qualifying inpatients who have been exposed but are asymptomatic (with a negative OR positive test for SARS-CoV-2).
  2. Place an order for Casirivimab & Imdevimab or Bamlanivimab & Etesevimab or Sotrovimab in POE.
  3. Obtain approval from Antimicrobial Stewardship (AST). The medication will only be approved for use 8 am. to 6 p.m.
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 may be given to patients who have previously received the COVID-19 vaccine. If an unvaccinated patient receives monoclonal antibody therapy, they should defer vaccination for 90 days following antibody administration. If a partially vaccinated patient receives monoclonal antibody therapy, they should defer the second dose for 90 days following antibody administration. This is based on the estimated half-life of monoclonal antibody therapy, but there is little data to guide this recommendation.

Dosing and Route of Administration
For treatment of symptomatic COVID-19:

<table>
<thead>
<tr>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>700 mg BAM, 1400 mg ETES combo IV once</td>
<td>600 mg CASI, 600 mg DEV combo IV once</td>
<td>500 mg IV once</td>
</tr>
</tbody>
</table>

For prophylaxis following exposure to SARS-CoV-2:

<table>
<thead>
<tr>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>700 mg BAM, 1400 mg ETES combo IV once</td>
<td>600 mg CASI, 600 mg DEV combo IV OR SC once</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

- Ongoing exposure for longer than 4 weeks after the initial dose (in patients unable to mount an immune response to SARS-CoV-2 vaccination): 300 mg of casirivimab and 300 mg of imdevimab combo intravenous OR via subcutaneous injection once every 4 weeks for the duration of ongoing exposure

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

<table>
<thead>
<tr>
<th></th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reactions</td>
<td>Similar rates to placebo (1%)</td>
<td>Slightly higher rates than placebo (4% vs 2%)</td>
<td>Similar rates to placebo (1%)</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Urticaria or general rash occurred at similar rates to placebo (1-2%)</td>
<td>Urticaria or general rash occurred at similar rates to placebo (&lt;0.1%)</td>
<td>Rash mild or moderate at 2%, comparable to placebo</td>
</tr>
<tr>
<td>General:</td>
<td>Nausea, dizziness, headache: similar rates to placebo, 1%</td>
<td>Nausea, dizziness, headache similar rates to placebo, 1%</td>
<td>Diarrhea, nausea, dizziness similar rates to placebo, 1%</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Company</th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly and Company</td>
<td>1-317-277-0853</td>
<td>1-888-876-2736</td>
<td>1-919-287-2902</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:mailindata_gsmtindy@lilly.com">mailindata_gsmtindy@lilly.com</a></td>
<td><a href="mailto:medical.information@regeneron.com">medical.information@regeneron.com</a></td>
<td><a href="mailto:WW.GSKAEReportingUS@gsk.com">WW.GSKAEReportingUS@gsk.com</a></td>
</tr>
<tr>
<td>Phone</td>
<td>1-855-545-5921</td>
<td>1-844-734-6643</td>
<td>1-866-475-2684</td>
</tr>
</tbody>
</table>

Requirements for the EUA by Discipline

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

<table>
<thead>
<tr>
<th>EUA Detailed Fact Sheets</th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUA Detailed Fact Sheets</td>
<td>Fact Sheet for Health Care Providers</td>
<td>Fact Sheet for Health Care Providers</td>
<td>Fact Sheet for Health Care Providers</td>
</tr>
<tr>
<td>Frequently Asked Questions (FAQ) for EUA</td>
<td>FAQ on EUA for bamlanivimab-etesevimab</td>
<td>FAQ on EUA for casirivimab-imdevimab</td>
<td>FAQ on EUA for sotrovimab</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>English Language</th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>English Language</td>
<td>FDA Patient/Caregiver Fact Sheet</td>
<td>FDA Patient/Caregiver Fact Sheet</td>
<td>FDA Patient/Caregiver Fact Sheet</td>
</tr>
<tr>
<td>Spanish Language</td>
<td>Spanish language Patient/Caregiver Fact Sheet</td>
<td>Spanish language Patient/Caregiver Fact Sheet</td>
<td>Spanish language Patient/Caregiver Fact Sheet</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Materials for preparation</td>
<td>• Materials for preparation</td>
<td>• Materials for preparation</td>
</tr>
<tr>
<td>o PVC or PE-lined PVC, sterile prefilled 100 mL NS infusion bag</td>
<td>o PVC or PE-lined PVC, sterile prefilled 100 mL NS infusion bag</td>
<td>o PVC or PE-lined PVC, sterile prefilled 100 mL NS infusion bag</td>
</tr>
<tr>
<td>o One 700 mg/20 mL bamlanivimab vial</td>
<td>o One 1332 mg (120 mg/mL) casirivimab vial</td>
<td>o One 500 mg sotrovimab vial</td>
</tr>
<tr>
<td>o Two 700 mg/20 mL etesevimab vials</td>
<td>o One 1332 mg (120 mg/mL) imdevimab vial</td>
<td>• Allow vials to reach room temperature for ~20 minutes; do not expose to direct heat or shake</td>
</tr>
<tr>
<td>• Allow vials to reach room temperature for ~20 minutes; do not expose to direct heat or shake</td>
<td>• Allow vials to reach room temperature for ~20 minutes; do not expose to direct heat or shake</td>
<td>• Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.</td>
</tr>
<tr>
<td>• Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into prefilled NS bag</td>
<td>• Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing 100 mL 0.9% NS</td>
<td>• Inspect the vial visually for particulate matter and discoloration prior to preparation. Should either be observed, the vial must be sequestered. Sotrovimab is a clear, colorless or yellow to brown solution.</td>
</tr>
<tr>
<td>• Discard any product remaining in vials</td>
<td>• Preparation of 600 mg casirivimab and 600 mg imdevimab (usual dose)</td>
<td>• Gently swirl the vial several times before use without creating air bubbles. Do not shake the vial.</td>
</tr>
<tr>
<td>• Gently invert IV bag by hand ~10 times to mix; do not shake</td>
<td>o If using co-formulated vial, add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into prefilled NS infusion bag</td>
<td>• Withdraw 8 mL of sotrovimab from one vial and inject into the 100 mL prefilled infusion bag</td>
</tr>
<tr>
<td>• Label with beyond use date/time</td>
<td>o If using casirivimab and imdevimab individual vials add 5 mL of casirivimab and 5 mL of imdevimab prefilled NS infusion bag</td>
<td>• Label with beyond use date/time</td>
</tr>
<tr>
<td></td>
<td>o Preparation of 300 mg casirivimab and 300 mg imdevimab (maintenance dose – rarely used)</td>
<td></td>
</tr>
</tbody>
</table>
Subcutaneous Preparation Instructions (FOR CASIRIVIMAB AND IMDEVIMAB ONLY)

Note: This route of administration is limited to care sites where intravenous therapy is not feasible (e.g., free-standing clinics).

1. Remove the casirivimab and imdevimab 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 casirivimab and imdevimab vial(s) 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 pale yellow.

3. Casirivimab and imdevimab should be prepared using the appropriate number of syringes. Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
   a. For preparation of 600mg casirivimab and 600mg imdevimab
      i. If using co-formulated vial, withdrawal 2.5 mL solution per syringe into FOUR separate syringes
      ii. If using casirivimab and imdevimab individual vials, withdrawal 2.5 mL solution per syringe into TWO separate syringes of casirivimab and TWO separate syringes of imdevimab
   b. For preparation of 300mg casirivimab and 300mg imdevimab
      i. If using co-formulated vial, withdrawal 2.5 mL solution per syringe into TWO separate syringes
      ii. If using casirivimab and imdevimab individual vials, withdrawal 2.5 mL solution per syringe into ONE syringe of casirivimab and ONE separate syringes of imdevimab

4. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.

Storage

- Bamlanivimab & Etesevimab
  o 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. DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT. Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours and at room temperature (20°C to 25°C [68°F to 77°F]) and for up to 7 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature prior to administration.

- Casirivimab & Imdevimab
  o Intravenous: The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
  o Subcutaneous: The prepared syringes should be administered immediately. If immediate
administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 4 hours or at room temperature up to 25°C (77°F) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

- **Sotrovimab**
  - 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 of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.
**Nursing**

Review Fact Sheets as necessary (provided above)

Intravenous infusion instructions are the same for all three products:

<table>
<thead>
<tr>
<th></th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
</table>
| **Intravenous infusion** | PVC or PE-lined PVC infusion set  
  In-line or add-on 0.20/0.22 micron PES filter | Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times.  
**Do not** invert the infusion bag. Avoid forming air bubbles. Administer entire contents  
via pump or gravity with a minimum infusion time of **30 minutes** |
| **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 the end of the infusion. |

**Subcutaneous administration instructions (Casirivimab & Imdevimab only)**

Note: This route of administration is limited to care sites where intravenous therapy is not feasible (e.g., free-standing clinics).

1. For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes and prepare for subcutaneous injections.
2. For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes and prepare for subcutaneous injections.
3. Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
4. When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. **DO NOT** inject into skin that is tender, damaged, bruised, or scarred.
5. Clinically monitor patients after injections and observe patients for at least 1 hour.

Report medication errors or serious adverse events to the primary team; see section below for more information.

**General Drug Related Warnings**

Infusion 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 based on severity
Essential medications to be kept in the infusion 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

Additional Information

Major studies informing the EUA

<table>
<thead>
<tr>
<th>Study</th>
<th>Bamlanivimab &amp; Etesevimab</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase 3 RCT vs placebo</td>
<td>Phase three RCT (1200mg dose or 2400mg dose vs placebo)</td>
<td>RCT (1200mg dose vs placebo)</td>
</tr>
<tr>
<td>Population</td>
<td>n=~1040 Outpatients COVID + mild-moderate disease at risk of advanced disease</td>
<td>N=~4000 Outpatients COVID + mild-moderate disease at risk of advanced disease</td>
<td>N=~1500 outpatients with household COVID exposure</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Combined: hospitalization or all-cause mortality at day 29</td>
<td>Combined: 28d hospitalization or all-cause mortality</td>
<td>Symptomatic COVID at 28d</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primary endpoint occurred in 2.1% (treatment) vs. 7.0% (placebo) P&lt;0.001</td>
<td>2400mg dose: 71.3% reduction in primary endpoint vs placebo [1.3% vs 4.6%] 1200mg dose: 70.4% reduction in primary endpoint vs placebo [1.0% vs 3.2%]</td>
<td>81.4% risk reduction in primary endpoint vs placebo 11/753 [1.5%] vs. 59/752 [7.8%]</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Change in SARS-CoV-2 viral load</td>
<td>Time to resolution of symptoms</td>
<td>Time to resolution of symptoms</td>
</tr>
<tr>
<td>Outcome</td>
<td>Log change in VL compared with placebo -1.20 (-1.46, -0.94)</td>
<td>14 days vs. 10 days (placebo)</td>
<td>1.2 vs. 3.2 weeks (placebo)</td>
</tr>
</tbody>
</table>
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 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, 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.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Bamlanivimab &amp; Etesevimab*</th>
<th>Casirivimab &amp; Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha (B.1.1.7)</td>
<td>Fully active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Beta (B.1.351)</td>
<td>Inactive</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Gamma (P.1)</td>
<td>Inactive</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Delta (B.1.617.2)</td>
<td>Fully active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Delta Plus (AY.1)</td>
<td>Visit w/Lilly</td>
<td>Visit w/RGN</td>
<td>Fully active</td>
</tr>
<tr>
<td>Epsilon (B.1.427/B.1.429)</td>
<td>Etesevimab active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Iota (B.1.526)</td>
<td>Less active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Kappa/no designation (B.1.617.1/B.1.617.3)</td>
<td>Etesevimab active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Lambda (C.37)</td>
<td>Fully active</td>
<td>Fully active</td>
<td>Fully active</td>
</tr>
<tr>
<td>Mu (B.1.621)</td>
<td>Inactive</td>
<td>Fully active</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Bamlanivimab and etesevimab is inactive against some SARS-CoV-2 variants. People who have traveled to, resided in, or had close contact with an infected individual from an area where the frequency of resistant variants to bamlanivimab and etesevimab exceeds 5% should not receive bamlanivimab and etesevimab. This list is available from the FDA.
Authors: Howard Gold MD; Christopher McCoy, PharmD, Daniel Taupin, MD

Advisors:

<table>
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<th>Humera Kausar, MD</th>
<th>AJH LHMC LHMC NEBH Beverly</th>
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<td>Amanda Cote, PharmD</td>
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<td>Lahey Health Beverly</td>
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Sponsor: Richard Nesto, MD, Anthony Weiss
Approval Body: BILH Infectious Diseases Subcommittee
BILH P&T Committee

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Revisions: Aug 2021, Sep 2021, Nov 2021
Next Review Date: December 2021

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