
Outpatient administration guide for healthcare providers

2 SEPTEMBER 2021
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1. Introduction to Monoclonal Therapy
Summary of COVID-19 Therapeutics

Scope of this Implementation Guide

No Illness
- Exposed / Asymptomatic Infected
  - Not hospitalized, no limitations

Early Symptomatic
- Not hospitalized, with limitations

Hospital Admission
- Hospitalized, no acute medical problems
- Hospitalized, not on oxygen
- Hospitalized, on oxygen

ICU Admission
- Hospitalized, high flow oxygen/non-invasive ventilation
- Hospitalized, mechanical ventilation/ECMO

Monoclonal Antibodies for post-exposure prophylaxis
- Casirivimab + Imdevimab (RGN)

Monoclonal Antibodies for treatment
- Bamlanivimab + Etesevimab1 (Lilly)
- Casirivimab + Imdevimab (RGN)
- Sotrovimab (GSK/Vir)

Key: ✅ FDA approved  🌟 EUA issued

1. Not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: https://www.fda.gov/media/151719/download
Potential Mechanisms for the Clinical Effects of Monoclonal Antibodies

**a) Bind to Virus**

1) Block cell uptake

2) Block membrane fusion

**b) Bind to Virus**

3) Deliver to immune

_Destruction_

**Impede ability to replicate**

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Source: Nature

- Monoclonal antibodies (mAbs) directly neutralize the COVID-19 virus and are intended to prevent progression of disease
- mAbs are most effective when given early in infection
Monoclonal Antibodies and Variants of Concern

- Estimated biweekly proportions of the most common SARS-CoV-2 lineages circulating in the U.S available from the CDC variant proportions data tracker\(^1\). Providers should assess variant prevalence in their geographic area when choosing mAb.

- Information on variants of concern updated in Section 15 of FDA fact sheets\(^2,3\).

### Table 3: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested*</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N + E484K + N501Y</td>
<td>215(</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K</td>
<td>46(</td>
</tr>
<tr>
<td>B.1.427/1.429 (California origin)</td>
<td>L452R</td>
<td>9(</td>
</tr>
<tr>
<td>B.1.526 (New York origin)</td>
<td>E484K</td>
<td>31(</td>
</tr>
</tbody>
</table>

*For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity (as per test) is listed. For B.1.351, P.1 and B.1.427/1.429, spike variants reflective of the consensus sequence for the lineage were tested.

\(^{a}\) No change: <5-fold reduction in susceptibility.

\(^{b}\) Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage. No activity observed at the highest concentration tested for the P.1 variant.

\(^{c}\) Etesevimab retains activity against this variant.

\(^{d}\) Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using pseudotyped VLPs with the E484K substitution only.

### Table 1: Authentic SARS-CoV-2 and Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Sotrovimab

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested*</th>
<th>Fold Reduction in Susceptibility (Pseudotyped VLP)</th>
<th>Fold Reduction in Susceptibility (Authentic Virus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N + E484K + N501Y</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>B.1.427/1.429 (California origin)</td>
<td>L452R</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>B.1.526 (New York origin)</td>
<td>E484K</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
<tr>
<td>B.1.617 (India origin)</td>
<td>L452R + E484Q</td>
<td>no change(^a)</td>
<td>no change(^a)</td>
</tr>
</tbody>
</table>

1. CDC Variant tracker
2. FDA fact sheets: REGEN-COV\(^\text{Tm}\) (www.fda.gov/media/145611/download); bamlanivimab and etesevimab (https://www.fda.gov/media/145802/download)
# Review of Clinical Data (I/II)

<table>
<thead>
<tr>
<th>Date</th>
<th>Source</th>
<th>Trial design / patients</th>
<th>Reported outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2021</td>
<td>JAMA</td>
<td>RCT, n = 577</td>
<td>• 70% reduction in hospitalization for high-risk patients</td>
<td>Lilly trial (Ph 2)</td>
</tr>
<tr>
<td>Feb 2021</td>
<td>Website</td>
<td>Observational</td>
<td>• 50% decrease in hospitalizations, 40% decrease in emergency department visits</td>
<td>St. Luke’s</td>
</tr>
<tr>
<td>Mar 2021</td>
<td>Lilly</td>
<td>RCT, n = 769</td>
<td>• 87% relative reduction vs. placebo in hospitalizations / death</td>
<td>Lilly trial (Ph 3)</td>
</tr>
<tr>
<td>Mar 2021</td>
<td>Regeneron</td>
<td>RCT, n = 4,567</td>
<td>• 70% relative reduction vs. placebo in hospitalizations / death</td>
<td>Regen. trial (Ph 3)</td>
</tr>
</tbody>
</table>
| Mar 2021 | NEJM        | Observational, n not listed | • 4.2% hospitalization rate for those treated with mAbs vs. 9-14.6% reported for untreated high-risk  
• Only 13% felt symptoms progressed after therapy | Houston Methodist             |
| Mar 2021 | Medrxiv     | Observational, n = 234 matched, | • Patients receiving mAb had 69% lower odds of hospitalization or mortality, and 50% lower odds of hospitalization or ED visit without hospitalization  
• 6% hospitalization in treated vs. 16.2% untreated, | UPMC                         |
| Apr 2021 | Medrxiv     | Observational, n = 270 treated, 328 untreated | • 1.9% of treated patients presented to E.D. / required hospitalization vs. 12% of untreated | ASPR                         |
# Review of Clinical Data (II/II)

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<tr>
<th>Date</th>
<th>Source</th>
<th>Trial design / patients</th>
<th>Reported outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr 2021</td>
<td>Medrxiv</td>
<td>Observational, n = 2,818</td>
<td>- Hospitalization rate was 4.4% for patients who received MAB therapy w/in 0-4 days, 5% w/in 5-7 days, and 6.1% w/in ≥8 days of symptom onset (p = 0.15)</td>
<td>Northwell Health</td>
</tr>
<tr>
<td>May 2021</td>
<td>Medrxiv (preprint)</td>
<td>RCT, n = 4,057</td>
<td>- 2400mg &amp; 1200mg drugs sig. reduced hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; p&lt;0.0001] and 70.4% reduction [1.0% vs 3.2%; p=0.0024], respectively)</td>
<td>Regen. trial</td>
</tr>
<tr>
<td>Jun 2021</td>
<td>JAMA</td>
<td>RCT, n = 1175</td>
<td>- Bam significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (p&lt;.001) at skilled nursing/assisted living facilities</td>
<td>Lilly trial (Ph 3)</td>
</tr>
<tr>
<td>Aug 2021</td>
<td>NEJM</td>
<td>RCT, n = 2475</td>
<td>- Subcutaneous REGEN-COV prevented symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons (p&lt;0.001)</td>
<td>Regen. trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Among participants who became infected, REGEN-COV reduced duration of symptomatic disease and high viral load (p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>
### Monoclonal Antibody Safety Data

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Reported Safety Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bamlanivimab and etesevimab</strong></td>
<td></td>
</tr>
</tbody>
</table>
| [https://www.covid19.lilly.com/bam-ete/hcp/clinical-data](https://www.covid19.lilly.com/bam-ete/hcp/clinical-data) | • Blaze 1 Trial Phase 3 Data (bamlanivimab 700mg and etesevimab 1400mg): Treatment n=511, Placebo n=258  
  ▪ Deaths: 0 in treatment group, 4 in placebo group  
  ▪ Adverse reactions observed in those who received bamlanivimab and etesevimab were anaphylaxis (n=1, 0.7%) and infusion-related reactions (n=16, 1.1%). The most common treatment-emergent adverse events included nausea, dizziness, and pruritis. No treatment-emergent events occurred in more than 1% of participants and were comparable with placebo |
| **REGEN-COV**            |
| **casirivimab and imdevimab** |
| [https://www.regencov.com/hcp/clinical-information/safety](https://www.regencov.com/hcp/clinical-information/safety) | • ~16,000 subjects studies in clinical trials (~13,500 received intravenous infusion and 2,500 subcutaneous injection)  
  ▪ COV-2067 (Phase 3 trial of non-hospitalized subjects receiving intravenous administration): 0/827 patients in the treatment arm had a reaction requiring termination of the infusion (urticaria, pruritis, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash)  
  ▪ COV-2069 (PEP in COVID-19 negative individuals exposed to a household member; n= 1311): Injection site reactions (erythema, pruritis) 4% in treatment group/ 2% in placebo group. No cases of anaphylaxis |
| **sotrovimab**           |
  ▪ Infusion related reactions, including immediate hypersensitivity, observed in 1% of treatment group and 1% of placebo group  
  ▪ Most common treatment-emergent adverse events (all were grade 1- mild, or grade 2-moderate): rash (2%) diarrhea (1%), no other events were reported at a higher rate with treatment compared to placebo |

*For non-severe infusion-related reactions, consider slowing or stopping the infusion and administer appropriate medications*
2. Overview of Emergency Use Authorization
Q: What is an emergency use authorization and how is it being used to respond to COVID-19

A: In certain types of emergencies, the FDA can issue an emergency use authorization, or EUA, to provide more timely access to critical medical products (including medicines and tests) that may help during the emergency when there are no adequate, approved, and available alternative options.

The EUA process is different than FDA approval, clearance, or licensing because the EUA standard may permit authorization based on significantly less data than would be required for approval, clearance, or licensing by the FDA. This enables the FDA to authorize the emergency use of medical products that meet the criterial within weeks rather than months to years.

EUAs are in effect until the emergency declaration ends but can be revised or revoked as we evaluate the needs during the emergency and new data on the product’s safety and effectiveness, or as products meet the criteria to become approved, cleared, or licensed by the FDA.

# Indications for Outpatient COVID-19 mAbs

## Monoclonal Antibody Indications and Routes of Administration

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>TREATMENT of Mild to Moderate COVID-19 Infection within 10 days of symptom onset in patients with high risk of progression to severe disease</th>
<th>POST-EXPOSURE PROPHYLAXIS for individuals who are not fully vaccinated or immunocompromised, with high risk of progression to severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>bamlanivimab and etesevimab(^1)</td>
<td>Dose: 700 mg bamlanivimab and 1400 mg etesevimab(^***) Route: Intravenous administration Post-administration monitoring: 60 minutes</td>
<td>N/A</td>
</tr>
<tr>
<td>(Eli Lilly)(^***)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>casirivimab and imdevimab(^2)</td>
<td>Dose: casirivimab 600mg and imdevimab 600mg Route: Intravenous is preferred route, however subcutaneous injection may be utilized in situations where there would be a delay in intravenous administration Post-administration monitoring: 60 minutes</td>
<td>Dose: casirivimab 600mg and imdevimab 600mg Route: Intravenous or subcutaneous Post-administration monitoring: 60 minutes</td>
</tr>
<tr>
<td>(REGEN-COV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotrovimab(^3)</td>
<td>Dose: sotrovimab 500mg Route: Intravenous Post-administration monitoring: 60 minutes</td>
<td>N/A</td>
</tr>
<tr>
<td>(Glaxo Smith Kline)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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** *** Based on the most currently available data, [bamlanivimab and etesevimab are now authorized](https://www.fda.gov/media/151719/download) in all U.S. states, territories, and jurisdictions (9/2/21).

Refer to product Emergency Use Authorizations for detail on indications and administration:

1. [Fact Sheet for Health Care Providers Emergency Use Authorization of Bamlanivimab and Etesevimab](https://www.fda.gov/media/145802/download)
2. [Fact Sheet for Health Care Providers Emergency Use Authorization of REGEN-COVTM (casirivimab and imdevimab)](https://www.fda.gov/media/145611/download)
3. [Fact Sheet for Health Care Providers Emergency Use Authorization of Sotrovimab](https://www.fda.gov/media/149534/download)
Provider and Patient EUA Fact Sheets

• Each product under EUA also has an FDA fact sheet for providers and one for patients and caregivers
  
  - bamlanivimab and etesevimab
    - Provider fact sheet: https://www.fda.gov/media/145802/download
    - Patient fact sheet: https://www.fda.gov/media/145803/download
  
  - casirivimab and imdevimab (REGEN-COV)
    - Provider fact sheet: https://www.fda.gov/media/145611/download
    - Patient fact sheet: https://www.fda.gov/media/145612/download
  
  - sotrovimab
    - Provider fact sheet: https://www.fda.gov/media/149534/download
    - Patient fact sheet: https://www.fda.gov/media/149533/download
Key Caveats for Monoclonal Antibodies with Emergency Use Authorization (EUA)

- The EUAs are for the use of the unapproved COVID-19 monoclonal antibody products:
  - bamlanivimab and etesevimab
  - casirivimab and imdevimab
  - sotrovimab

- The listed mAbs are investigational drugs that have not been approved by the FDA for any use and should not be considered the standard of care for treatment of patients with COVID-19.

- Clinical trials studying the safety and efficacy of monoclonal antibodies in COVID-19 are ongoing.

- Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to monoclonal antibodies under EUA.
Administration site **does not need to be a clinical trial site** to administer product.

A **signed consent form is not needed** to administer products under EUA. Patient fact sheets are provided and risks/benefits discussed with patient as outlined in the EUA.

**No clinical data reporting required** beyond established FDA mechanisms for tracking and reporting serious adverse events.

**HHSProtect TeleTracking data reporting required** on utilization of product.
3. Site and Patient Logistics
Administration Can Occur Across a Wide Variety of Models

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Ambulatory center</th>
<th>Nursing homes</th>
<th>Mobile sites</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospital-based infusion centers</td>
<td>• Infusion centers</td>
<td>• Skilled nursing facilities</td>
<td>• Bus/trailer</td>
<td>• At patient's home</td>
</tr>
<tr>
<td>• Emergency departments</td>
<td>• Urgent care clinics</td>
<td>• Long-term care facilities</td>
<td>• Other mobile sites</td>
<td></td>
</tr>
<tr>
<td>• Converted space within hospital for COVID</td>
<td>• Dialysis centers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infusion centers</td>
<td>• Alternate care sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alternate care sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Mobile sites:
  - Bus/trailer
  - Other mobile sites

- Home:
  - At patient's home
Examples of staff plans *(recommended positions may vary depending on the state scope of practice for Paramedics as it related to Subcutaneous and or Intravenous administration of medications or mAbs)*

- **8-10 bed mAb infusion/observation site**
  - 1 physician / advanced practitioner (present or available via telemedicine)
  - 2 Nurses
  - 1 Nurse or Paramedic
  - 2 Paramedics
  - 1 flex position – administrative/ logistics/ runner

- **Single station or mobile visit Subcutaneous administration site**
  - 1 physician / advanced practitioner (present or available via telemedicine)
  - 1 Nurse / Paramedic per single mobile visit or single station

Average patient (door to door) visit can range from 80-120 minutes
Site Preparation

• Collect administration site location(s), address, and points of contact
  ▪ For mobile or deployed teams, identify the point of contact at the administration site and make contact
  ▪ Site will need dedicated space for isolation of COVID-19 patients¹
  ▪ Rededication of existing clinical space is permitted under the CMS Hospital Without Walls Initiative

• Ensure a patient scheduling and referral process is in place

• Identify and understand which therapeutics will be administered

• Determine who is responsible for ordering the monoclonal antibody administration
  ▪ Referring provider
  ▪ On-site or telemedicine provider
  ▪ Standing order

• Brief administration team with site objectives

• Team training
  ▪ Site workflow
  ▪ Monoclonal administration
  ▪ Managing adverse reactions

¹ Select recommendations for outpatient setting, for more information reference CDC guidelines
Pathway to Monoclonals: Patient with Confirmed COVID-19 Infection

- Treatment likely most beneficial to patients if given **early in symptom progression**
- EUA requires administration of **treatment as soon as possible after confirmed positive test result and within 10 days of symptom onset**
- Strong **partnership and communication** between patients and HCP to get right treatment to right patients at right time
- Fast testing turnaround needed, to efficiently **identify positive tests** and **schedule for treatment**

**Example of timeline which would fulfill EUA requirements**

<table>
<thead>
<tr>
<th>Onset of symptoms</th>
<th>Clinical visit and diagnostic test</th>
<th>Confirmed positive test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 days post symptom onset</td>
<td>≤ 2 days post diagnostic test</td>
<td>≤3 days post positive test result</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment needed within 10 days of symptom onset**

- Testing sites should recommend COVID+ patients that are high risk confer with their HCP on potential suitability for Tx

Please reference EUA factsheet for specific treatment guidelines including recommended treatment window
Potential Patient Pathways for Post-Exposure Prophylaxis (PEP)

• Referral through contact tracing
• Providers diagnosing COVID-19 positive patients encouraging them to refer household members and close contacts for evaluation to PEP (with specifics on pathway for evaluation in the relevant geographic area)
• Providers caring for immunocompromised patients (e.g., transplant patients, chemotherapy patients, etc.) educating them on PEP and the need for quick evaluation if exposed

Key Stakeholders for Communication of PEP

• Primary Care providers
• Specialty providers caring for immunocompromised patients
• Public health officials
• Home health care teams caring for COVID-19 positive patients
• Contact tracers
• Urgent care and emergency department providers diagnosing symptomatic patients with COVID-19 (Referring symptomatic patients for treatment and encouraging patients to reach out to close contacts regarding PEP in addition to reporting to health department for contact tracing)
## Patient Flow for Outpatient mAbs Product

**Scenario 1: Confirmed positive patient referred for treatment**

### Pre-treatment

- **Confirm documentation of COVID-19 infection via either**
  - Participant-provided lab report
  - Medical record lab report
  - Direct communication from a provider or laboratory

- **Discuss treatment with patient**
  - Ensure patient meets treatment requirements and understands risks

- **Schedule the patient to come in for treatment ASAP**
  - Provide guidance on site visit protocols to patients
  - Provide patient education on what to expect with administration

*Pre-treatment steps should be completed via telemedicine as possible (~30 mins)*

### Treatment

- **Pre-book time for administration space and follow clear protocol for coming onsite**
  - Ensure operationally ready to receive and treat the patient
  - Use CDC recommended practices to minimize exposure to others

- **Provide treatment to patient**
  - Infusion duration up to ~1 hr\(^1\) with an additional 1 hr of observation post infusion (checks during infusion and observation)
  - Infusion pumps or gravity-based infusion acceptable
  - Subcutaneous administration if appropriate per EUA\(^2\)

- **Ensure preparation for administration reactions as unlikely but possible side effect**
  - Infusion rate may be reduced based on patient circumstances
  - Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA

### Post-treatment

- **Discharge patient immediately following monitoring completion**
  - Follow clear protocol to minimize risk of exposure to others

- **Post-treatment care encouraged to be via telemedicine as possible**
  - Normal follow-up care, no special data tracking requirements

---

1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
2. Reference EUA for route of administration
## Patient Flow for Outpatient mAbs Product

### Scenario 2 and 3: Patient arrives for testing at site with unknown diagnosis

**Pre-treatment**

Direct patient to typical testing process for site (onsite or offsite)
- Quick response testing needed for early diagnosis to enable early treatment

Assuming patient discharged to await test results, once patient confirmed positive outreach on treatment (~30 mins):
- Discuss treatment with patient
  - Ensure patient meets treatment requirements and understands risks
  - Provide guidance on administration and site visit protocols to patients
- Schedule the patient to come in for treatment ASAP
- Pre-treatment discussion and scheduling should be via telemedicine as possible

In case of point-of-care rapid testing, consider same-day administration. Needs
- Isolated location for patient to wait
- Availability of treatment space and staff

**Treatment**

Pre-book time for administration space and follow clear protocol for coming onsite
- Ensure operationally ready to receive and treat the patient
- Use CDC recommended practices to minimize exposure to others

Provide treatment to patient
- Infusion duration up to ~1 hr\(^1\) with an additional 1 hr of observation post infusion (checks during infusion and observation)
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- Subcutaneous administration if appropriate per EUA\(^2\)

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- Infusion rate may be reduced based on patient circumstances
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Discharge patient immediately following monitoring completion
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Post-treatment care encouraged to be via telemedicine as possible
- Normal follow-up care, no special data tracking requirements

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1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
2. Reference EUA for route of administration

---

\(^{1}\) Reference EUA for route of administration

---

\(^{2}\) Reference EUA fact sheet for dilution and infusion timing
Patient Flow for Post-Exposure Prophylaxis

**Pre-treatment**

Confirm eligibility for PEP
- Patient meets CDC high risk exposure criteria¹
- Patient is not fully vaccinated or immunocompromised²

Discuss treatment with patient
- Ensure patient meets treatment requirements and understands risks

Schedule the patient to come in for treatment ASAP
- Provide guidance on site visit protocols to patients
- Provide patient education on what to expect with administration

**Treatment**

Pre-book time for administration space and follow clear protocol for coming onsite
- Ensure operationally ready to receive and treat the patient
- Use CDC recommended practices to minimize exposure to others

Provide treatment to patient
- Infusion duration up to ~1 hr¹ with an additional 1 hr of observation post infusion (checks during infusion and observation)
- Infusion pumps or gravity-based infusion acceptable
- Subcutaneous administration if appropriate per EUA²

Ensure preparation for administration reactions as unlikely but possible side effect
- Infusion rate may be reduced based on patient circumstances
- Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA

**Post-treatment**

Discharge patient immediately following monitoring completion
- Follow clear protocol to minimize risk of exposure to others

Post-treatment care encouraged to be via telemedicine as possible
- Normal follow-up care, no special data tracking requirements

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4. Team Responsibilities
Administration Site Team Members

- Administration Site Leadership
- Administrative personnel
- Clinical Team
  - Composition dependent on state and local regulations and route of mAb administration (intravenous or subcutaneous)
  - Medical Provider (MD/NP/PA) on-site or available via telemedicine
Administration Site Leadership

- Ensure ordering process is implemented
- Ensure required elements for administration are available
  - Personnel
  - Supplies
  - Administrative support
  - Identified site for administration
- Determination of scheduling process/logistics if treatment and PEP provided at the same site (as not all patients are COVID-positive)
- Determine mechanism for reimbursement of administration fees (product provided by the US Government is provided at no cost)
- Consider mechanism for interpreter services if patients are non-English speaking
- Delegate or perform administrative responsibilities
  - Direct ordering
  - Reporting of adverse events
  - Utilization reporting
Distribution – Direct Ordering for mAb Products Under EUA

- HHS/ASPR continues to manage the distribution of mAb products under EUA as stated in the FDA Letters of Authorization

- Given the current supply of product, casirivimab / imdevimab and bamlanivimab / etesevimab can be requested via direct ordering for all sites

- Questions regarding the direct order process: HHS: COVID19Therapeutics@hhs.gov

Information on direct order process available on PHE.gov.

Sites receiving monoclonal antibody will follow established mechanisms for tracking and reporting serious adverse events

- Events that are potentially attributable to monoclonal antibody use must be reported to the FDA
  - Refer to the Fact Sheet for Healthcare Providers as part of EUA for guidance
  - Complete and submit a MedWatch form or complete and fax FDA Form 3500 to report

Site must maintain records regarding use of the monoclonal antibody by patients

- **Inventory information**: e.g., lot numbers, quantity, receiving site, receipt date, product storage
- **Patient information**: e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered

Ensure that any records associated with this EUA are maintained for inspection upon request
Sites are required to report utilization of product to HHS through their state or TeleTracking system.

First-time users will receive enrollment and reporting instructions in an e-mail from protect-noreply@hhs.gov with the subject line of “Invitation: HHS TeleTracking COVID-19 Portal.”

This email provides step-by-step instructions to access the Portal for the first time.

If you do not receive an email in the next 48 hours, please contact TeleTracking Technical Support at hhs-protect@teletracking.com.
<table>
<thead>
<tr>
<th>Site of Care</th>
<th>Payable by Medicare</th>
<th>Expected Patient Cost-Sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Hospital</td>
<td>✔️</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Hospital or &quot;Hospital without Walls&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Physician Office/Infusion Center</td>
<td>✔️</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Nursing Home (See third bullet in Key Facts on CMS enforcement discretion)</td>
<td>✔️</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Home</td>
<td>✔️</td>
<td>No patient cost-sharing</td>
</tr>
</tbody>
</table>

1 Services must be furnished within the scope of the product’s FDA authorization or approval and within the provider’s scope of practice.
2 Under the Hospital Without Walls initiative, hospitals can provide hospital services in other healthcare facilities and sites that would not otherwise be considered to be part of a healthcare facility; or can set up temporary expansion sites to help address the urgent need to increase capacity to care for patients.
3 Cost-sharing may apply to Medicare beneficiaries when they receive care from a provider that doesn’t participate in Medicare.

Expected Payment to Providers: Key Facts

- Medicare payment for monoclonal antibody products to treat COVID-19 is similar across sites of care, with some small differences.
- Medicare pays for the administration of monoclonal antibody products to treat COVID-19. For example, Medicare will pay a national average of approximately $450 for the administration of certain monoclonal antibody products. Home infusion is reimbursed at a higher rate.
- CMS will exercise enforcement discretion to allow Medicare-enrolled immunizers working within their scope of practice and subject to applicable state law to bill directly and receive direct reimbursement from the Medicare program for administering monoclonal antibody treatments to Medicare Part A Skilled Nursing Facility residents.
- Medicare will pay the provider for these monoclonal antibody products when they are purchased by the provider. Medicare won’t pay if the product is given to the provider for free by, for example, a government entity.
- When purchased by the provider, Medicare payment is typically at reasonable cost or at 95% of the Average Wholesale Price (an amount determined by the manufacturer). These payment amounts vary depending on which type of provider is supplying the product. Original Medicare will pay for these products for beneficiaries enrolled in Medicare Advantage.
- For more specific information about Medicare payments to providers for these monoclonal antibody products, please see these Frequently Asked Questions.

bamlanivimab and etesevimab Product Codes

Q0245:
• Long descriptor: Injection, bamlanivimab and etesevimab, 2100 mg

M0245:
• Long Descriptor: intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring

M0246:
• Long Descriptor: intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence

Regen-COV Product Codes

Q0243:
• Long descriptor: Injection, casirivimab and imdevimab, 2400 mg

M0243:
• Long Descriptor: intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring

M0244:
• Long Descriptor: intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring in the home or residence

sotrovimab Product Codes

Q0243:
• Long descriptor: Injection

CMS.gov: Monoclonal Antibody COVID-19 Infusion – Monoclonal Antibody Products to Treat COVID-19
Ensure appropriate infection control practices in place based on latest CDC guidelines, e.g.:

- Have patient wait to enter the site until scheduled time for treatment
- Ensure patient wearing a mask or face covering before entering the building
- Escort patient directly to room, limit transport and movement of the patient outside of the room
- As all patients treated are confirmed positive for COVID-19, multiple patients may be treated simultaneously in one area.
- Medical and support personnel entering room need to wear sufficient PPE based on CDC guidelines
- Room should undergo appropriate cleaning and surface disinfection before it is returned to routine use

Select recommendations for outpatient setting, for more information reference CDC guidelines
Clinical Team Responsibilities: Patient Intake

- If MD/NP/PA is on site, they can provide order for mAb after patient intake/screening completed.

- Patient intake (healthcare provider type determined by state regulations/scope of practice):
  - Ensure patient is masked for duration of encounter.
  - Patient registration completed.
  - Vital signs obtained (ensure patient does not require oxygen unless on home 02, therefore making them ineligible for mAb therapy and requiring escalation of care).
  - Eligibility criteria reviewed:
    - Treatment eligibility criteria.
    - Post exposure Prophylaxis Criteria.
  - Patient Fact Sheet provided to patient prior to administration of mAb.
Clinical Team Responsibilities

- mAb preparation for subcutaneous or intravenous administration
- Ensure patient privacy is maintained in accordance with HIPPA
- mAb administration
- Post-administration monitoring (60 minutes for all patients)
- Response to administration reaction
- Patient discharge and follow-up instructions
5. Monoclonal Antibodies: Indications and Administration
Indications for Monoclonal Therapy & Appropriate mAbs for Treatment

- Active COVID-19 Infection in high risk individuals with mild to moderate symptoms
  - REGEN-COV (casirivimab and imdevimab)
  - bamlanivimab/etesevimab
  - sotrovimab (commercially available)

- Post-Exposure Prophylaxis in vulnerable persons (i.e. not fully vaccinated or immunocompromised) who are at high risk for progression to severe COVID-19
  - REGEN-COV (casirivimab and imdevimab)

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1 Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on FDA website: https://www.fda.gov/media/151719/download
Indications for Treatment of Patients with Confirmed COVID-19 Infection

- bamlanivimab and etesevimab
- casirivimab and imdevimab
- sotrovimab
mAb Eligibility Criteria for TREATMENT of Mild-Moderate Covid-19 Infection in High Risk Individuals

Products granted EUA for mild to moderate COVID-19 cases early in infection, who are at high risk for progressing to severe COVID-19 and/or hospitalization; with following criteria:

- Adult or pediatric (> 12 years of age and weighing at least 40kg) patient
- Confirmation via positive PCR or antigen test
- Treatment as soon as possible following positive viral test and within 10 days of symptom onset
- Patient symptomatic but not yet progressed to require hospitalization or oxygen therapy (or increase from baseline chronic oxygen therapy)

Monoclonal antibodies given EUA for mild to moderate symptoms of COVID-19 are not authorized for use in patients:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

Benefit of treatment with mAbs has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
HIGH RISK FACTORS FOR TREATMENT AND POST-EXPOSURE PROPHYLAXIS WITH mAbs INCLUDE, BUT ARE NOT LIMITED TO:

- Older age (for example \( \geq 65 \) years of age)
- Obesity or being overweight (for example, adults with BMI \( \geq 25 \), or if age 12-17, have BMI \( \geq 85^{th} \) percentile for their age and gender based on CDC growth charts)
- Pregnancy
- Chronic Kidney Disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital abnormalities)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of mAb therapy is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, visit the CDC website:

- [CDC’s Clinical Growth Charts](https://www.cdc.gov/growthcharts/clinical_charts.htm)
Monoclonal Antibodies: Post-Exposure Prophylaxis (PEP)
REGEN-COV Eligibility for POST-EXPOSURE PROPHYLAXIS**

REGEN-COV (casirivimab and imdevimab) is authorized for post-exposure prophylaxis of COVID-19 in individuals who are:

- Adult or pediatric (≥ 12 years of age and weighing at least 40kg) patient **at high risk for progressing to severe disease or death (see high risk criteria)**
- Not fully vaccinated¹ or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications²) AND
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC³ OR
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of COVID-19 in other individuals in the same institutional setting (for example, nursing homes, prisons) [see limitations of authorized use]

**Limitations of Authorized Use:**

- *Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19*
- *REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19*

Resources: Monoclonal Eligibility for POST-EXPOSURE PROPHYLAXIS

1 Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson’s Janssen vaccine). See this CDC website for more details on Have You Been Fully Vaccinated? (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated)


3 Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details on Quarantine and Isolation (https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html)
Monoclonal Antibody Administration
Product will be shipped refrigerated (2-8° C) to your location by USG distribution partners.

Product should be stored refrigerated (2-8° C) before use.

Target shelf-life for product ~10 months at minimum, follow guidance from manufacturer on expiration dates and product turnover.

Prepared IV solutions are intended for immediate patient administration. If not used immediately:

- Solutions may be held at refrigerated conditions for example:
  - bamlanivimab and etesevimab no more than 24 hours
  - REGEN-COV no more than 36 hours
  - sotrovimab no more than 24 hours

- Solutions may be held at ambient light and room temperature conditions (including preparation, solution hold, infusion and flush) for example:
  - bamlanivimab and etesevimab no more than 7 hours
  - REGEN-COV no more than 4 hours
  - sotrovimab no more than 4 hours

Prepared subcutaneous doses of Regeneron should be administered immediately. If not used immediately:

- Syringes may be held at refrigerated conditions for no more than 4 hours and room temperature for no more than 4 total hours.

Please adhere to all guidelines for storage and use provided by manufacturer of EUA product.
mAb Preparation

Note: product can be prepared for infusion and subcutaneous administration bedside by any qualified medical professional

Administration preparation process:
- Prepare sterile infusions in a manner consistent with local laws, regulations, guidelines and policies
- Obtain new vial(s) and/or IV bags if the drug product contains any visible particulate matter

Needs for space to prepare mAb drug:
- Dedicated preparation area with sufficient capacity onsite or nearby

Acceptable equipment for mAb drug storage:
- Refrigerated storage (2-8° C)
- Temperature control mechanism including temperature monitoring process

Please see EUA manufacturer fact sheet for drug-specific requirements
General Guidelines for bamlanivimab/etesevimab Dosing, Dilution, and Administration

### Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing 50 kg or More

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>310 mL/hr</td>
<td>21 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>41 minutes</td>
</tr>
<tr>
<td>250 mL</td>
<td>310 mL/hr</td>
<td>60 minutes</td>
</tr>
</tbody>
</table>

*a 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.*

### Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>310 mL/hr</td>
<td>21 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>41 minutes</td>
</tr>
</tbody>
</table>

Notes for Eli Lilly: BAMLANIVIMAB MUST BE ADMINISTERED TOGETHER WITH ETESEVIMAB AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY. 

**Note:** not all 50mL & 100mL saline bags will allow addition of 60mL of bam / ete – please ensure bag allows for mixing

# casirivimab/imdevimab Formulations and Dose Preparation

**Dose:** REGEN-COV (casirivimab 600mg and imdevimab 600mg)*

<table>
<thead>
<tr>
<th>Administration Route</th>
<th>Single Product Vials</th>
<th>REGEN-COV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong></td>
<td>casirivimab (REGN10933) <strong>5ml total</strong> (from 2.5 or 11.1 mL vials)</td>
<td>10 mL total</td>
</tr>
<tr>
<td>(Mixed and administered per EUA instructions)</td>
<td>imdevimab (REGN10987) <strong>5ml total</strong> (from 2.5 or 11.1 mL vials)</td>
<td></td>
</tr>
<tr>
<td>Intravenous infusion is strongly recommended for treatment of active infection. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For Post-Exposure prophylaxis either subcutaneous injection or intravenous route can be used.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subcutaneous</th>
<th>Two syringes with 2.5 mL each of casirivimab (REGN10933) <strong>(total of 5 ml casirivimab)</strong></th>
<th>Four syringes each containing 2.5mL REGEN-COV for a <strong>total of 10mL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two syringes with 2.5 mL each of imdevimab (REGN10987) <strong>(total of 5 ml imdevimab)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*REGEN-COV (casirivimab 1200mg and imdevimab 1200mg) dosing no longer authorized under EUA*
Guidelines for REGEN-COV Repeat Dosing for Post-Exposure Prophylaxis

• For individuals whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination

• The initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion

• Followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.
General Guidelines for REGEN-COV Intravenous Dosing, Dilution, and Administration

Dilution Instructions for REGEN-COV (600 mg Casirivimab and 600 mg Imdevimab) for intravenous infusion

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th>
<th>Preparing Using Co-Formulated Casirivimab and Imdevimab Vial</th>
<th>Preparing Casirivimab and Imdevimab Using Individual Vialsa</th>
</tr>
</thead>
</table>
| 50 mL                                             | Add 10 mL of co-formulated Casirivimab and Imdevimab (1 vial) into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below | Add:  
• 5 mL of Casirivimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL)  
• 5 mL of Imdevimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL)  
And inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below. |
| 100 mL                                            |                                                            |                                                             |
| 150 mL                                            |                                                            |                                                             |
| 250 mL                                            |                                                            |                                                             |

Table 2: Recommended Administration Rate for Casirivimab and Imdevimab for Intravenous Infusion

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag used</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mLa</td>
<td>180 mL/hr</td>
<td>20 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>21 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>250 mL</td>
<td>310 mL/hr</td>
<td>50 minutes</td>
</tr>
</tbody>
</table>

* The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) or REGEN-COV™ (casirivimab and imdevimab)  
General Guidelines for REGEN-COV Subcutaneous Dosing and Administration

Administration Instructions for REGEN-COV (600 mg Casirivimab and 600mg Imdevimab) for subcutaneous injection

<table>
<thead>
<tr>
<th>Prepare 600 mg of Casirivimab and 600 mg of Imdevimab</th>
<th>Preparation of 4 Syringes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Casirivimab and Imdevimab Co-formulated Vial</td>
<td>Withdraw 2.5 mL solution per syringe into FOUR separate syringes.</td>
</tr>
</tbody>
</table>
| Using Casirivimab and Imdevimab Individual Vials    | • Casirivimab: Withdraw 2.5 mL solution per syringe into TWO separate syringes.  
• Imdevimab: Withdraw 2.5 mL solution per syringe into TWO separate syringes.  
For total of 4 syringes. |

Intravenous infusion is strongly recommended for treatment of active infection. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

For Post-Exposure Prophylaxis either subcutaneous or intravenous route can be used.

Preparation and Administration:

• Obtain four 3mL or 5mL luer lock syringes and four 21 gauge 1½ inch transfer needles
• Withdraw 2.5 mL into each syringe per preparation instructions. Prepare all four syringes at the same time.
• Replace the 21 gauge transfer needle on each syringe with a 25-gauge or 27-gauge needle for subcutaneous injection
• 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.
• It is recommended that providers use different quadrants of the abdomen, upper thighs, or back of the upper arms to space apart each injection
• DO NOT inject into skin that is tender, damaged, bruised, or scarred

Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV™ (casirivimab and imdevimab)
REGEN-COV Preparation for Subcutaneous Injection

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 vial(s).**

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 a new vial must be used. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. 600 mg of casirivimab and 600 mg of imdevimab should be prepared using 4 syringes (see table below). Obtain four 3-mL or 5-mL polypropylene Luer lock syringes with Luer connection and four 21-gauge, 1½-inch transfer needles.

2. Withdraw 2.5 mL into each syringe (total of 4 syringes) (see table below). Prepare all 4 syringes at the same time.
   - If individual vials of casirivimab and imdevimab are being used, consider labeling syringes during preparation to ensure the two syringes of casirivimab and two syringes of imdevimab are identifiable.

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

4. This product is preservative-free and therefore, 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 ºC to 8 ºC (36 ºF to 46 ºF) for no more than four hours or at room temperature up to 25 ºC (77 ºF) for no more than four total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Additional Educational Resources and Videos Available at:

REGEN-COV™
https://www.regencov.com/hcp/dosing/dosing-administration
• The prescribing healthcare provider and/or the provider’s designee are responsible for mandatory reporting of all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. These adverse events must be reported within seven calendar days from the onset of the event.

• Healthcare facilities and providers must report therapeutics information and demonstrate adequate utilization via data reported through HHS Protect, TeleTracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

• **MedWatch adverse event reports can be submitted to the FDA**, by submitting a postage-paid Form FDA 3500 and returning by mail/fax, or by calling 1-800-FDA-1088 to request a reporting form. In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc via fax (1-888-876-2736) or email (medical.information@regeneron.com).

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**REGEN-COV Subcutaneous Injection Sites**

- **Back of the upper arm**
- **Abdomen**
  - Except for within two inches of the navel
- **Upper thigh**
Utilizing Previously Shipped REGEN-COV (casirivimab and imdevimab) Dose Pack

Previously created REGEN-COV Dose Pack contains 2 patient courses as of the June 2021 EUA¹ (enclosed information sheet has dosing from prior EUA). 1 patient course is 5ml casirivimab/5ml imdevimab

The dose pack may be utilized for two doses. Once punctured, the vials should be discarded after 4 hours.

Refer to the “Regeneron Important Prescribing Letter” for more information

Please contact Regeneron Medical Affairs with any questions about using existing inventory to treat patients at 1-844-734-6643

June 3, 2021 updated EUA authorized dose change
FROM casirivimab 1200 mg and imdevimab 1200mg TO casirivimab 600mg and imdevimab 600mg

Preparation

Sotrovimab is supplied in a single-dose vial and must be diluted prior to administration. Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique.

- Gather the materials for preparation
  - Polyvinyl chloride (PVC) or polyolefin (PO), sterile prefilled infusion bag. Choose one of the following sizes:
    - prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
    - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and a fresh solution prepared.
  - Sotrovimab is a clear, colorless or yellow to brown solution
- Gently swirl the vial several times before use without creating air bubbles. Do not shake the vial.
- Withdraw 8 mL sotrovimab from one vial and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection.
- Discard any product remaining in the vial.
- 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.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately.
  - If immediately administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

- Infuse over 30 minutes
- Do NOT deliver via IV push or IV bolus
- Monitor patient for 60 minutes after infusion

Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Sotrovimab
Post-Administration Monitoring

- Per EUA, “Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete”
- Provide education on follow-up, required isolation per CDC guidelines after COVID-19 exposure or diagnosis, red flags for seeking emergency care
- Respond to severe adverse events/ anaphylaxis
- “Discharge” patient after one hour post-administration monitoring if stable and without symptoms of severe adverse reaction
- Report any severe adverse events as required by the FDA through the process outlined in the EUA
• **Monoclonal antibodies may only be administered** in settings in which health care providers have immediate access to medications to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

• Early identification of anaphylaxis. Symptoms may include:
  - Respiratory: throat tightness, stridor, hoarseness, wheezing, respiratory distress, coughing, trouble swallowing/drooling, nasal congestion/drainage, sneezing
  - Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, cramps
  - Cardiovascular: dizziness, fainting, tachycardia, hypotension, cyanosis, pallor, flushing
  - Skin/mucosal: hives, erythema, itching, swelling of eyes, lips, tongue, mouth, face, or extremities
  - Neurologic: agitation, convulsions, altered mental status, sense of impending doom
  - Other: sudden increase in secretions, urinary incontinence
Managing Adverse Reactions: Medications and Equipment

• **Should be available** at all sites:
  - Epinephrine (e.g., prefilled syringe or autoinjector)
  - H1 antihistamine (e.g., diphenhydramine, cetirizine)
  - Blood pressure monitor

• **If feasible**, include at sites (not required)
  - Oxygen
  - Bronchodilator (e.g., albuterol)
  - H2 antihistamine (e.g., famotidine, cimetidine)
  - Intravenous fluids
  - Intubation kit
  - Adult-sized pocket mask with one-way valve (CPR mask)

Adapted from [CDC Interim Considerations: Preparing for the potential management of anaphylaxis at COVID-19 vaccination sites](https://www.cdc.gov/vaccines/covid-19/downloads/IntermConsid-Anaphylaxis-covid19-vaccineSites.pdf)
Please note… EUA guidelines continue to evolve

Please reference EUA fact-sheets for latest treatment guidelines and information, including:

- mAb dosing
- Administration routes
- Dilution requirements and infusion time for intravenous administration
COVID-19 Vaccination after mAb Administration

The current recommendation based on CDC guidance is to delay COVID-19 vaccination for 90 days after administration of mAb

CDC Advisory Committee on Immunization Practices: (Updated August 21, 2021)

People who previously received passive antibody therapy

“Currently, there are no data on the safety and efficacy of COVID-19 vaccines in people who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment or post-exposure prophylaxis. Based on the estimated half-life of such therapies and evidence suggesting that reinfection is uncommon within the 90 days after initial infection, vaccination should be deferred for at least 90 days after receiving monoclonal antibodies or convalescent plasma. This is a precautionary measure until additional information becomes available, to avoid potential interference of the antibody therapy with vaccine-induced immune responses. This recommendation applies to people who receive passive antibody therapy before receiving any vaccine dose; any vaccine dose after the initial vaccine dose should be deferred for at least 90 days following receipt of the antibody therapy. Receipt of passive antibody therapy in the past 90 days is not a contraindication to receipt of COVID-19 vaccine. COVID-19 vaccine doses received within 90 days after receipt of passive antibody therapy do not need to be repeated.”

Vaccinated people who subsequently develop COVID-19

For people who have received one or more doses of COVID-19 vaccine and subsequently experience SARS-CoV-2 infection, prior receipt of a COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment, or corticosteroid administration) or timing of such treatments.

If a person has SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥14 days after they complete all recommended doses of a currently FDA-approved or FDA-authorized COVID-19 vaccine (defined as a COVID-19 vaccine breakthrough case), CDC encourages local health departments, healthcare professionals, and clinical laboratories to:

- Request the respiratory specimen be held for further testing
- Report the case to the state health department where the individual resides for further investigation and reporting to the national system

CDC’s Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States
6. Suggested Supplies
## Site Supplies Needed

### Infrastructure
- Seating area with appropriate spacing for patients to receive mAb
- Steel table for product preparation
- Privacy screens if needed
- Protocol/outline for patient flow (written protocol not required however patient flow and infection control should be addressed at each administration site)
- Emergency response plan (written plan not required, however all staff should be aware of the plan for emergency response)

### General Supplies
- Infusion Reaction Kit
- Refrigerator
  - Optional to store prepared solution onsite
- Sharps container
- Biohazard disposal bag
- Trash bins and liners
- Disposable disinfecting wipes
- Hand sanitizer
- Thermometer probe covers (if required)
- 70% alcohol wipes
- Paper towels

### PPE
- NIOSH-certified, disposable N95 filter facepiece respirators or better
- Gloves in appropriate sizes
- Gowns
- Surgical face masks for patients
- Eye and face protection (e.g. goggles, safety glasses, face shields)

### Patient Intake
- Vital signs machine
- Pulse oximeter
- Thermometer
- Copies of eligibility checklist for treatment/PEP

### Administrative
- Site-specific documentation
- Patient fact sheets to provide each patient (copies in English, Spanish and other appropriate languages)

### Administration Supplies - Subcutaneous
- Alcohol wipes
- 3 or 5mL luer lock syringes (4 required for each patient for subcutaneous administration)
- Appropriate needles for product preparation and subcutaneous administration
  - 21 gauge 1.5 inch needles for product transfer
  - 25 or 27 gauge needles for subcutaneous administration (4 per each patient course)

### Administration Supplies - Intravenous
- IV poles
- Alcohol wipes
- 2x2 gauze pads
- Adhesive bandages
- Medical tape
- Tegaderm bio-occlusive dressing
- Absorbent underpads (blue pads)
- Normal saline bags for mixing/administration- 50-250 mL
- IV administration sets: PVC infusion set with/without DEHP containing 0.2 or 0.22 micron polyethersulfone (PES) in-line filter
- IV catheters
- IV extension set tubing
- 3mL saline syringes
- Needles – stainless steel 18ga
- Optional: Transilluminator (vein finder)
8. Links and Resources
Product-Specific Playbooks for Monoclonal Antibody Administration

**Eli Lilly bamlanivimab/etesevimab Antibody Playbook**

Objective to help sites of care operationalize a Bamlanivimab/Etesevimab antibody response to COVID-19 across varying infusion sites of care


**Regeneron EUA guidebook**

Provides additional detail on administration requirements for Regeneron mAbs product

https://www.regencov.com/content/pdf/guidebook.pdf

**Guide for sotrovimab Use**

Provides additional detail on administration of sotrovimab


July 2021 EUA Update Pending
Helpful Links

• **Federal Monoclonal Antibody Site**
  - https://www.phe.gov/mAbs

• **PHE COVID-19 Toolkit**
  - https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/toolkit.aspx

• **CMS Hospital Without Walls**

• **CMS Monoclonal Antibody Reimbursement**
  - **Coverage of Monoclonal Antibody Products to Treat COVID-19**
  - **Monoclonal Antibody COVID-19 Infusion: Monoclonal Antibody Products to Treat COVID-19**

• **CDC COVID Data Tracker**
  - https://covid.cdc.gov/covid-data-tracker/#datatracker-home

• **Clinical Trial Information for Patients not Eligible for EUA**
  - **Lilly Clinical Trials**
  - **Regeneron Clinical Trials**
    - https://www.regeneron.com/covid19
Helpful Resources for Clinicians

- **COVID-19 Monoclonal Antibody Eligibility Checklist: Treatment and PEP**

- **COVID-19 Monoclonal Antibody Checklist for Subcutaneous and Intravenous Administration**
  - https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/covid19-mAb-checklist-subcutaneous-intravenous-administration.aspx

- **Subcutaneous Injection Instructions**

- **EMS Template Protocol**

- **Guidelines on Vaccination after mAb administration**
### Educational Opportunities:

**Project Echo Sessions on Monoclonal Antibodies**

- **Educational Opportunities**: Project Echo
- **Sessions on Monoclonal Antibodies**

<table>
<thead>
<tr>
<th>Project Echo Presentation Title</th>
<th>Date</th>
<th>Link</th>
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</thead>
<tbody>
<tr>
<td>Monoclonal Antibodies - Bamlanivimab</td>
<td>2/9/2020</td>
<td><a href="https://www.youtube.com/watch?v=YKjRgQGI-Nw">https://www.youtube.com/watch?v=YKjRgQGI-Nw</a></td>
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<td>Equitable Access- Outpatient Infusion Site</td>
<td>2/16/2020</td>
<td><a href="https://www.youtube.com/watch?v=0ZZixudBeog">https://www.youtube.com/watch?v=0ZZixudBeog</a></td>
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<td>Monoclonal Antibodies: OSU experience</td>
<td>12/3/2020</td>
<td><a href="https://www.youtube.com/watch?v=p3JsR9wasEU">https://www.youtube.com/watch?v=p3JsR9wasEU</a></td>
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<tr>
<td>Where are we now? mAb Therapy in Michigan</td>
<td>1/6/2021</td>
<td><a href="https://www.youtube.com/watch?v=CnniyMayiXc">https://www.youtube.com/watch?v=CnniyMayiXc</a></td>
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<tr>
<td>Managing infusion reactions Northwell Health Experience</td>
<td>1/27/2021</td>
<td><a href="https://www.youtube.com/watch?v=zaem2mDUvKE">https://www.youtube.com/watch?v=zaem2mDUvKE</a></td>
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<td>EMS involvement in mAb infusion programs</td>
<td>2/1/2021</td>
<td><a href="https://www.youtube.com/watch?v=CZnCv4ktmnw">https://www.youtube.com/watch?v=CZnCv4ktmnw</a></td>
</tr>
<tr>
<td>Achieving Speed and Scale in FQHCs and Health Systems</td>
<td>2/10/2021</td>
<td><a href="https://hsc.unm.edu/echo/_docs/hhs-covid/2.10.21-manini.pdf">https://hsc.unm.edu/echo/_docs/hhs-covid/2.10.21-manini.pdf</a>; <a href="https://hsc.unm.edu/echo/_docs/hhs-covid/2.10.21-webb.pdf">https://hsc.unm.edu/echo/_docs/hhs-covid/2.10.21-webb.pdf</a></td>
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<tr>
<td>Regional Approaches to mAb Administration-Operationalizing Partnerships</td>
<td>2/17/2021</td>
<td><a href="https://www.youtube.com/watch?v=h-ewtgAO1gl">https://www.youtube.com/watch?v=h-ewtgAO1gl</a></td>
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<tr>
<td>Equity and Underserved Populations</td>
<td>2/24/2021</td>
<td><a href="https://www.youtube.com/watch?v=I4Geh2hSisM2Q">https://www.youtube.com/watch?v=I4Geh2hSisM2Q</a></td>
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<tr>
<td>Clinical trials update and Patient/Provider Outreach</td>
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<tr>
<td>Partnering with Urgent Care Centers to Increase Access and Utilization of COVID mAbs: NYC Health</td>
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<td>Where We’re Headed: Variants and COVID-19 Therapy</td>
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<tr>
<td>Real world effectiveness and implementation of COVID-19 monoclonal antibodies</td>
<td>4/22/2021</td>
<td><a href="https://www.youtube.com/watch?v=s2kfRGL4uJ4">https://www.youtube.com/watch?v=s2kfRGL4uJ4</a></td>
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For information on upcoming sessions visit: [HHS ASPR Clinical Rounds](https://hsc.unm.edu/echo)
Federal Infusion Sites (December 2020-January 2021)

- **COVID**: Nation's first infusion center meant to reduce impact on El Centro Regional Medical Center
- **Free COVID-19 antibody treatment available in Tucson (Arizona public media)**
- **Las Vegas becomes third US city with federally supported clinic offering COVID-19 antibody treatment**

Clinical Sites

- **"It's like a miracle:" Monoclonal antibody use soars over 300% in Michigan (5/21)**
  - https://www.michiganradio.org/post/its-miracle-monoclonal-antibody-use-soars-over-300-michigan
- **Chula Vista COVID Site Offering free monoclonal antibody treatments to all (6/21)**
- **EDs administer mAb therapy to high-risk COVID-19 patients (4/21)**
- **COVID-19 Monoclonal antibody study combo helps high-risk people avoid hospital (Mayo Clinic Study 9/2021)**
- **Over 40,000 COVID-19 patients in Florida have had monoclonal antibody treatments. Is it working?**
- **East Tennessee Children’s Hospital using monoclonal therapy to treat children with Covid**
Questions?

https://phe.gov/mAbs
Email: covid19therapeutics@hhs.gov

Thank you!