Federal Response to COVID-19: Monoclonal Antibody Playbook

Outpatient administration playbook for healthcare leadership

3 JUNE 2021

Updates 3 June 2021:
Updated Regeneron dosing - REGEN-COV (600mg casirivimab and 600mg imdevimab)
Updated Regeneron routes of administration
Regeneron co-formulation
Introduction

Comprehensive checklist overview

Activity 1: Define facilities and patient visit logistics
- Site will need dedicated outpatient COVID-19 treatment space
- Alternate site of care allowances and needs
- Manage patient flow in accordance with CDC guidelines
- Pharmacy Needs
- Testing Needs
- High level guidance on product shipping and storage

Activity 2: Ensure sufficient supplies
- Site supplies needed: Standard infusion supplies are required

Activity 3: Develop plan for staffing and personnel
- Treating patients needs support of healthcare providers, pharmacist, and nurses

Activity 4: Review drug administration process
- Multiple treatment pathways for symptomatic COVID-19 patients to receive care

Activity 5: Prepare for reimbursement and drug ordering
- Reimbursement process for mAbs therapeutic under Emergency Use Authorization (EUA)

Activity 6: Reporting process
- Reporting Needs
Introduction
This playbook is intended to support sites interested in administering COVID-19 monoclonal antibody (mAb) treatment under EUA including but not limited to:

- Existing hospital or community-based infusion centers
- Existing clinical space (e.g. urgent care, emergency depts)
- Ad hoc new infusion sites (e.g. "hospitals without walls")
- Long-term care facilities
- Home infusions

This playbook continues to evolve as other treatments and administration methods become available. We hope this playbook will be used to help healthcare facilities implement monoclonal antibody treatment in an outpatient setting for those with COVID-19.
Context of mAbs outpatient administration playbook

Proven operationally challenging to run monoclonal antibodies clinical trials in outpatient setting for variety of reasons

Initial EUAs were granted for Eli Lilly and Regeneron products in November 2020 only for outpatient setting

Expanded eligibility criteria for administration of both Eli Lilly and Regeneron products were released in May 2021 for outpatient setting

Monoclonal antibody infusion has been successfully implemented in a variety of outpatient settings

Monoclonal antibody administration has been expanded to include subcutaneous administration of the Regeneron product as of June 2021

Scope of this playbook

Goal of playbook to articulate what is needed for outpatient administration at potential infusion sites:

- Supplies likely required for administration and potential challenges in procurement
- Personnel needed for administration
- Space and logistics needed to safely treat COVID-19 patients and protect others
- Drug administration process
- Reimbursement process
- Reporting process
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.

Product delivered via IV infusion or subcutaneous injection.

Evolving evidence demonstrates promise of mAb products in outpatient settings:

- Evidence from Eli Lilly mAb cocktail showed potential to reduce hospitalization and death in infected people if given early in infection (Phase 3 data of BLAZE-1 clinical trial).
- Phase 1 and 2 data from Regeneron mAb cocktail trial showed potential to decrease viral load and reduced medical visits in infected people if given early (Outpatient 2067 clinical trial).
- Phase 1/2/3 data from Regeneron mAb cocktail supported a revised dosage in the June 2021 EUA (revised dosing: 600 mg casirivimab/ 600mg imdevimab).
mAbs products now available under EUA therefore...

Administration site does not need to be a clinical trial site to administer product

Informed consent is not needed to administer products under EUA

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

TeleTracking data reporting required on utilization of product
Treatment eligibility

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 home oxygen therapy)

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: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

HIGH RISK FACTORS INCLUDE, BUT ARE NOT LIMITED TO:

- Older age (for example > 65 years of age)
- Obesity or being overweight (for example, adults with BMI > 25, or if age 12-17, have BMI > 85th 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 infection))
Monoclonal antibodies are under evaluation for additional indications

Participation encouraged in clinical trials to assess additional drugs and indications

Clinical trial information available at
https://www.combatcovid.hhs.gov

Lilly clinical trials:

Regeneron clinical trials:
https://www.regeneron.com/covid19

For Patients Not Eligible for Treatment Under EUA:
Consider Clinical Trials
EUA summary: bamlanivimab/ etesevimab (Eli Lilly)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab/ etesevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Bamlanivimab/etesevimab 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 bamlanivimab/etesevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab/ etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Bamlanivimab/etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

For additional information—please reference EUA factsheet.

Key caveats

The EUA is for the use of the unapproved products bamlanivimab/ etesevimab to treat COVID-19.

Bamlanivimab/etesevimab 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.

It is not yet known if bamlanivimab/ etesevimab are safe and effective for the treatment of COVID-19.

This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use, unless the authorization is terminated or revoked sooner.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to bamlanivimab/etesevimab.
EUA summary: REGEN-COV (casirivimab/imdevimab) (Regeneron)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab/imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death.

Casirivimab/imdevimab 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 casirivimab/imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab/imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

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

Casirivimab/imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

For additional information—please reference EUA factsheet.

Key caveats

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Casirivimab/imdevimab 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.

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This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use, unless the authorization is terminated or revoked sooner.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to casirivimab/imdevimab.
Reminder | CDC variants of concern and other lineages by state Providers should assess variant prevalence in their geographic area when choosing mAb therapeutic

- Estimated biweekly proportions of the most common SARS-CoV-2 lineages circulating in the U.S available from the CDC variant proportions data tracker

- Information on variants of concern updated in Section 15 of FDA fact sheets

Unweighted Proportions of Variants of Concern and Other Lineages by State or Jurisdiction

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<tr>
<th>State</th>
<th>B.1.1.7</th>
<th>B.1.351</th>
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<th>Other lineages</th>
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Variation proportions are based on representative CDC sequence data (NS3 = CDC-funded contract sequencing collected over a 4-week period ending May 8, 2021 for states with at least 300 sequences.

1. FDA factheets: casirivimab and imdevimab (https://www.fda.gov/media/145611/download); bamlanivimab and etesevimab (https://www.fda.gov/media/145802/download)
WHO announces simple, easy-to-say labels for SARS-CoV-2 Variants of interest and concern

Variants of Concern

A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; or
- Increase in virulence or change in clinical disease presentation; or
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

<table>
<thead>
<tr>
<th>WHO label</th>
<th>Pango lineage</th>
<th>GISAID clade/lineage</th>
<th>Nextstrain clade</th>
<th>Earliest documented samples</th>
<th>Date of designation</th>
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<tr>
<td>Alpha</td>
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<td>20I/S:501Y.V1</td>
<td>United Kingdom, Sep-2020</td>
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<td>Gamma</td>
<td>P.1</td>
<td>GR/501Y.V3</td>
<td>20J/S:501Y.V3</td>
<td>Brazil, Nov-2020</td>
<td>11-Jan-2021</td>
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WHO announces simple, easy-to-say labels for SARS-CoV-2 Variants of interest and concern... cont'd

## Variants of Interest

A SARS-CoV-2 isolate is a Variant of Interest (VOI) if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:

- has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR
- is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.

<table>
<thead>
<tr>
<th>WHO label</th>
<th>Pango lineage</th>
<th>GISAID clade/lineage</th>
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<td>GR</td>
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<td>Eta</td>
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<td>21A/S.154K</td>
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<td>4-Apr-2021</td>
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Based on what we have learned to date - early administration of treatment needs fast testing turnaround and patient scheduling

Planning required for "Test and treat" or "Test and refer" models

Overview
- 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>
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<tbody>
<tr>
<td>( \leq 3 \text{ days post symptom onset} )</td>
<td>( \leq 2 \text{ days post diagnostic test} )</td>
<td>( \leq 3 \text{ days post positive test result} )</td>
<td></td>
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</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
Key challenges to overcome to allow for successful administration of mAb in outpatient setting

Drug ordering and storage

Out of scope of this playbook

For Additional Information on Ordering Monoclonal Antibodies:
https://www.phe.gov/emergency/events/COVID19/healthcare-facilities/Pages/default.aspx#step3

Key challenges for administration and strategies for success

- Existing infusion centers currently treat immune-compromised patients and may not be the logical site for COVID-19 treatment
- Many sites are not traditionally outfitted to do infusions in outpatient setting (besides hospitals and ERs), however successful models have been demonstrated in a variety of outpatient settings (stand-alone mAb infusion sites, skilled nursing facilities, and home infusion)
- Subcutaneous administration of Regeneron is an alternate route when intravenous infusion is not feasible and would lead to delay in treatment (1-hour post administration monitoring is required after subcutaneous administration)
- Length of infusion process (infusion time may be up to ~1 hour infusion\(^1\) followed by 1 hour post-infusion monitoring) needing dedicated space and personnel. EUA revisions have allowed shorter infusion times. Patients must still be monitored for 1 hour post infusion
- Quick turn-around time for testing needed to diagnose patients within window for treatment (on site testing expedites infusion capabilities)

Please reference EUA factsheet for specific treatment guidelines

1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Federal Monoclonal Antibody Playbook

Objective to summarize requirements to administer monoclonal antibodies for healthcare facilities interested in administering the product


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
June 2021 Guidebook Update Pending
Please reference EUA fact-sheets for latest treatment guidelines and information, including:

- mAb dosing
- Administration routes
- **Dilution requirements and infusion time for intravenous administration**

Comprehensive checklist overview
Plan of action to administer monoclonal antibodies under outpatient EUA

Confirm your site wants to participate
- Review needs for treatment in outpatient settings
- Ensure site prepared to meet needs for treatment or willing to make required investments
- Confirm site leadership supportive of participation
  - Including senior clinical leadership
- Establish direct ordering account for monoclonal antibody product

Prepare your site and staff for outpatient mAbs administration
- Ensure sufficient supply of needed materials for storage and treatment
  - Administration supplies, resuscitation equipment, etc.
- Develop staffing and personnel plan to support treatment
- Allocate needed facilities and equipment to support administration
- Ensure existing infection prevention plan sufficient
  - Adjust existing plan if needed to safely manage patient flow
  - Consider potential security requirements if needed
- Review drug administration needs with staff
- Review and establish reimbursement process for administration fees
- Prepare for adverse events data tracking process

Develop procedures to identify and treat patients in timely manner
- Prepare for scheduling and routing of referrals from testing center or other sites to treatment
- Ensure administration site staff and providers are aware of outpatient treatment availability
- Ensure patient privacy (HIPAA compliant) maintained during process
- Communicate to patient that EUA issued for investigational treatment but does not constitute research on behalf of the administration site
Readiness checklist: Administration of outpatient mAbs under EUA

Allocate **dedicated space** and develop plan to **manage patient flow**
- Clear process for patients that are coming to clinical site including scheduling requirements
- Admission process for COVID-19 positive patients designed to minimize risk of spread per facility requirements / directions / guidelines
- Dedicated room available for treatment

Ensure **dedicated source of supplies**;
- Vital sign monitoring equipment, emergency medications
- IV Administration: IV kits, infusion chair, IV pole
- Subcutaneous administration: Needles and syringes required for dose preparation and administration

Assign **sufficient personnel** to meet expected demand
- Sufficient staffing plans in place for Nurse/IV tech, Provider, Pharmacist or other licensed medical professional
  - Likely need dedicated team to treat patients

Prepare for **drug administration** process
- Pre-visit: Clear treatment and monitoring plan developed for administration
- Treatment: Up to ~1-hour treatment for intravenous administration\(^1\) and 1-hour post-treatment observation for IV and subcutaneous routes
  - Emergency protocol defined for addressing potential infusion reactions or complications
- Post-treatment: Clear process for patient follow-up defined using telemedicine as possible

Ensure **process for reimbursement** in place (non-drug administrative costs)

Prepare for **reporting needs** for adverse events and record keeping

\(^1\) Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Activity 1: Define facilities and patient visit logistics
Site will need dedicated outpatient COVID-19 treatment space

Dedicated COVID-19 patient area with needed administration supplies
- Some sites using COVID-19 waiting rooms for monitoring post infusion
- Rededication of existing clinical space acceptable under CMS Hospital Without Walls Initiative

Immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the EMS, as necessary

Select recommendations for outpatient setting, for more information reference CDC guidelines
As part of **CMS Hospital Without Walls initiative**, hospitals can provide services outside of standard hospital settings

- **Other healthcare facilities** (e.g., urgent care clinics, doctors’ offices etc)
- **Remote locations or sites** not normally considered healthcare facilities, (e.g., patient home via telemedicine, hotels, community site, temporary tents)
- **Nursing home or home health services** also likely to be acceptable sites of administration

Alternate site of care will need **same core capabilities and supplies** as typical site of administration

- Facility and patient flow needs (page 18 and 20 of this document)
- Supplies needed on site (e.g., rescue medication, administration supplies, etc – page 27 of this document)

**Please reference CMS Hospitals Without Walls waivers and guidance for detailed information about program**
Important to manage patient flow in a healthcare setting

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 https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html
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:
- Functional pharmacy sink
- Refrigerated storage (2-8°C)
- Temperature control mechanism including temperature monitoring process

Please see EUA manufacturer fact sheet for drug-specific requirements
Outpatient monoclonal antibody treatments are to be administered as soon as possible following positive test result, and within 10 days of symptom onset.

Fast turn-around testing capabilities key to identify patients and treat within this window

- On-site point-of-care rapid testing or PCR tests ideal to provide quick diagnosis and treat patients on the same day
- Alternatives include partnership with off-site testing facility nearby with reliable and quick turnaround and robust patient tracking and reporting mechanism
  - Accelerated testing results turnaround likely recommended to allow for administration early in disease progression.

Please reference EUA factsheet for detailed treatment guidelines including recommended treatment window

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 (no further allocations to states are currently planned).

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

Information on direct order process available at phe.gov –

High level guidance on product shipping and storage

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
  - Eli Lilly **no more than 24 hours**
  - Regeneron **no more than 36 hours**
- Solutions may be held at ambient light and room temperature conditions (including preparation, solution hold, infusion and flush) for example
  - Eli Lilly **no more than 7 hours**
  - Regeneron **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**
Activity 2: Ensure sufficient supplies
Sites interested in providing outpatient administration of mAbs to COVID+ patients should:

1. Confirm sufficient supplies of administration materials
2. Proactively ensure items with long-lead times are sourced for your site

Ensure supplies sufficient to cover mAbs treatment in addition to day-to-day operations needs

Please reference EUA factsheet for final requirements

**List of suggested supplies (not exhaustive)**

**PPE**
- Gloves
- Gowns
- Eye and face protection (e.g. goggles, safety glasses, face shields)
- NIOSH-certified, disposable N95 filter facepiece respirators or better

**Administration supplies**
- Infusion chairs – *recommended only*
- Intravenous administration
  - IV pole
  - IV administration sets: PVC *infusion set with/without DEHP containing 0.2 or 0.22 micron polyethersulfone (PES) in-line filter*
    - IV and catheters
    - 3mL saline syringes
- Subcutaneous administration
  - Appropriately sized needles for preparation and administration
  - Appropriately sized syringes
- Alcohol wipes
- 2x2 gauze pads
- Adhesive bandages
- Tegaderm bio-occlusive dressing
- Absorbent underpads (blue pads)
- Extension set tubing
- Needles – stainless steel 18ga
- Sharps containers
- Transpore tape
- Transilluminator (vein finder)

**General supplies**
- Infusion Reaction Kit
- Vital signs equipment
- Crash cart or Emergency Medical Management Equipment and Backboard
- Refrigerator
  - Optional to store prepared solutions onsite
- Privacy screens
- Biohazard disposal bag
- Disposable disinfecting wipes
- Thermometer probe covers (if required)
- 70% alcohol wipes
- Paper towels
- Trash bins and liners
Activity 3: Develop plan for staffing and personnel
Prescribe monoclonal antibody to patient, answer questions and respond in case of emergency

- Licensed healthcare provider (MD/PA/NP)
- HCP will need to be on site or available via telehealth or phone for treatment
- At least 1 team member (nurse or healthcare provider) onsite should be able to respond to medical emergency (e.g., severe infusion reaction); any specific certifications based on state and healthcare facility regulations and policies

Prepare the infusion, answer questions and support with monoclonal antibody storage

- Pharmacy does not need to be physically located at the site of infusion
- Note the infusion can be prepared by any qualified medical professional

Administer patient infusion (up to ~1 hr) and monitor patient wellbeing (1 hr)

- May require 2 nurses to start infusion, nurse practitioner to oversee larger infusion unit (if needed)
- Experienced phlebotomist needed as often difficult to find vein in patients (often high BMI and dehydrated)

Please reference EUA factsheet for specific treatment guidelines including dilution and infusion time
<table>
<thead>
<tr>
<th>Role</th>
<th>Needed skills/profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient intake</td>
<td>Scheduling and administrative skills</td>
</tr>
<tr>
<td>Drug preparation</td>
<td>Pharmacist, pharmacy technician, or nurse or other HCP trained in IV preparation</td>
</tr>
<tr>
<td>Infusion: Start IV</td>
<td>Nurse or other alternate healthcare team member trained to begin an IV</td>
</tr>
<tr>
<td>Infusion: Administer infusion</td>
<td>Nurse or other alternate healthcare team member trained in administering an IV or subcutaneous injection (determined by route of administration)</td>
</tr>
<tr>
<td>Subcutaneous: Administer injections</td>
<td>Nurse or other alternate healthcare team member trained in monitoring for adverse reaction</td>
</tr>
<tr>
<td>Infusion monitoring</td>
<td>Nurse or other alternate healthcare team member trained in monitoring for adverse reaction</td>
</tr>
<tr>
<td>Post administration observation</td>
<td>Nurse or other alternate healthcare team member trained in monitoring for adverse reaction</td>
</tr>
<tr>
<td>Patient release</td>
<td>Administrative skills, or nurse or other alternate healthcare team member as required</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Person trained in COVID cleaning / disinfection</td>
</tr>
</tbody>
</table>
Activity 4: Review drug administration process
Three potential treatment pathways for symptomatic COVID-19 patients to receive care

Scenario 1: Patient tests positive and referred to site
- Treatment scheduled for administration as soon as possible following result
- Patient counseled and assents to treatment (if not completed earlier in process), then mAb administered
- Patient completes monitoring and leaves the facility, telemedicine follow-up

Scenario 2: Patient arrives for testing at site with unknown diagnosis
- Point-of-care testing performed, patient awaits results onsite
- Treatment scheduled for same day
- Patient counseled and assents to treatment (if not completed earlier in process), then mAb administered
- Patient completes monitoring and leaves the facility, telemedicine follow-up

Scenario 3: Patient arrives for testing at site with unknown diagnosis
- Patient tested, treatment discussed, sent home to await results
- If positive, proactive outreach to patients and treatment scheduled for administration as soon as possible following result
- Treatment needed as soon as possible following positive test result and ≤10 days from onset of symptoms
- Please reference EUA factsheet for exact treatment window
- Patient completes monitoring and leaves the facility, telemedicine follow-up
Patient flow for outpatient mAbs product

Scenario 1: Confirmed positive patient referred for treatment

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
</table>
| Confirm documentation of COVID-19 infection via either  
  • Participant-provided lab report  
  • Medical record lab report  
  • Direct communication from a provider or laboratory | 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 | 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 |
| Discuss treatment with patient  
  • Ensure patient meets treatment requirements and understands risks | 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\(^2\) |  |
| 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 | 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 |  |
| **Pre-treatment steps should be completed via telemedicine as possible (~30 mins)** |  |  |

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

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

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

---

1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
2. Reference EUA for route of administration
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>Drug*</th>
<th>Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</td>
<td>Maximum Infusion Rate</td>
</tr>
<tr>
<td>50 mL</td>
<td>310 mL/hr</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
</tr>
<tr>
<td>250 mL</td>
<td>310 mL/hr</td>
</tr>
</tbody>
</table>

* 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>Drug*</th>
<th>Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to an infusion bag and administer as instructed below</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</td>
<td>Maximum Infusion Rate</td>
</tr>
<tr>
<td>50 mL</td>
<td>310 mL/hr</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</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 – ensure bag allows for mixing

### Administration Route

<table>
<thead>
<tr>
<th>Single Product Vials</th>
<th>Co-Formulated REGEN-COV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong> (Mixed and administered per EUA instructions)</td>
<td>casirivimab (REGN10933) 5ml total (from 2.5 or 11.1 mL vials)</td>
</tr>
<tr>
<td></td>
<td>imdevimab (REGN10987) 5ml total (from 2.5 or 11.1 mL vials)</td>
</tr>
<tr>
<td><strong>Subcutaneous</strong></td>
<td>Two syringes with 2.5 mL each of casirivimab (REGN10933) (total of 5 ml casirivimab)</td>
</tr>
<tr>
<td></td>
<td>Two syringes with 2.5 mL each of imdevimab (REGN10987) (total of 5 ml imdevimab)</td>
</tr>
</tbody>
</table>
### General Guidelines for REGEN-COV Intravenous Dosing, Dilution, and Administration

**Dilution Instructions for REGEN-COV (600 mg Casirivimab and 600mg 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 Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td></td>
<td>Add:</td>
</tr>
<tr>
<td>100 mL</td>
<td>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</td>
<td>• 5 mL of casirivimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL)</td>
</tr>
<tr>
<td>150 mL</td>
<td></td>
<td>• 5 mL of imdevimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL)</td>
</tr>
<tr>
<td>250 mL</td>
<td></td>
<td>and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below</td>
</tr>
</tbody>
</table>

---

**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 mL&lt;sup&gt;a&lt;/sup&gt;</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>

<sup>a</sup> 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.

---

*600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.*

---

General Guidelines for REGEN-COV Subcutaneous Dosing and Administration

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

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


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

Activity 5: Prepare for reimbursement and ordering
Reimbursement process for mAbs therapeutic under EUA

Follow process for direct ordering procedures to receive mAb product

Under initial phase of treatment, drug cost likely to be paid by US government under advanced purchase agreements

Confirm internally with your site administration on reimbursement for non-drug costs (e.g., infusion services, pharmacy)

Please reference CMS resources for more information

CMS Monoclonal Reimbursement

CMS: Coverage of Monoclonal Antibody Products to Treat COVID-19

Medicare

<table>
<thead>
<tr>
<th>Site of Care1</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;2</td>
<td>✔</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Physician Office/Infusion Center</td>
<td>✔</td>
<td>No patient cost-sharing3</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>

1Services must be furnished within the scope of the product’s FDA authorization or approval and within the provider’s scope of practice.

2Under 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.

3Cost-sharing may apply to Medicare beneficiaries when they receive care from a provider that doesn’t participate in Medicare.

4Certain monoclonal antibody products to treat COVID-19 have been authorized under Food and Drug Administration Emergency Use Authorizations since November 10, 2020. More information including the level II HCPCS codes for the administration/infusion and post administration monitoring of these products can be found online in the Program Instruction.

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.

CMS billing codes


Eli Lilly product codes

M0245:
- Long descriptor: Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence
- Short descriptor: Bamlan and etesev infusion home

M0244:
- Long descriptor: Intraavenous infusion, bamlanivimab and etesevimab includes infusion and post administration monitoring in the home or residence
- Short descriptor: Bamlan and etesev infusion home

Regeneron product codes

M0243:
- Long descriptor: Intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring
- Short descriptor: Casiri and imdevi infusion

M0242:
- Long descriptor: Injection, casirivimab and imdevimab, 2400 mg
- Short descriptor: Casiri and imdevimab

M0244:
- Long descriptor: Intravenous infusion, casirivimab and imdevimab, 2100 mg
- Short descriptor: Casiri and imdevimab infusion

M0245:
- Long descriptor: Intravenous infusion, bamlanivimab and etesevimab, 2100 mg
Activity 6: Reporting process
Reporting needs

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.
Questions?
https://combatcovid.hhs.gov
Email: covid19therapeutics@hhs.gov

Thank you!