Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Background

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of monoclonal antibodies (mAbs), casirivimab and imdevimab (REGEN-COV) or bamlanivimab and etesevimab, for the treatment of mild to moderate coronavirus disease 2019 (COVID -19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS -CoV-2 (PCR) viral testing AND who are at high risk for progression to severe COVID-19 disease (including hospitalization or death) AND are within 10 days of symptom onset. In addition, the FDA expanded the EUA to include post-exposure prophylaxis for those individuals who are not vaccinated, incompletely vaccinated, or may not have adequate response to the vaccine AND are within 96 hours of high-risk exposure to someone with COVID-19. Monoclonal antibodies are used to neutralize the COVID-19 virus and intended to prevent progression of disease.

Confirm Eligibility

Any adult or pediatric patient (>12 years of age and weighing at least 40 kg) with one of the following high-risk factors for progressing to severe disease or death may receive mAbs.

High-Risk factors for development of severe COVID include, but are not limited to:

- Any medical condition or other factor, including race or ethnicity, that puts one at higher risk of progression to severe COVID-19
- 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)

Other medical conditions or factors may also place individual patients at high risk for progression to severe COVID-19 and authorization of monoclonal antibody 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).

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Treatment Dosing

Patients who are COVID-19 positive (positive PCR test, including fully vaccinated patients), within 10 days of symptom onset, AND with mild-to-moderate symptoms, AND not hospitalized due to COVID symptoms, AND not requiring oxygen or an increase in home oxygen therapy are eligible.

Post-Exposure Prophylaxis (PEP)

Individuals who are not fully vaccinated (two weeks after second dose of Pfizer or Moderna or single J&J vaccine) **OR** who are not expected to mount an adequate immune response to complete COVID-19 vaccination (for example, individuals with immunocompromising conditions or taking immunosuppressive medications) AND within the last 96 hours:

- Have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC (within 6 feet of someone for a cumulative total of 15 minutes or more over 24 hours); **OR**
- 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, long-term care facilities, or prisons).

Limitations of Authorized Use

- PEP with REGEN-COV or bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19
- REGEN-COV or bamlanivimab and etesevimab is not authorized for pre-exposure prophylaxis for prevention of COVID-19
- REGEN-COV or bamlanivimab and etesevimab is 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.
- Monoclonal antibodies, such as REGEN-COV or bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
- REGEN-COV or bamlanivimab and etesevimab are contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV or bamlanivimab and etesevimab.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Basic Equipment:

Equipment requirements may vary by medical direction. Follow your local requirements when determining the equipment needed for your treatment setting. The following equipment should be considered to ensure the most optimal care environment for patients receiving REGEN-COV. This list is not intended to substitute for your independent medical judgment.

Personal Protective Equipment

- Gloves/gowns
- Eye and face protection (e.g., goggles, safety glasses, face shields)
- NIOSH-certified facepiece respirators or better

Infusion Supplies

Administration set

- Sterile in-line 0.2/0.22 micron filter (may be integrated into administration set or separate add-on device)
- IV 0.9% normal saline and catheters
- Infusion pumps (if available)
- 3-mL saline syringes
- Appropriately sized syringes
- Alcohol wipes
- 2x2 gauze pads
- Adhesive bandages
- Occlusive dressing
- Absorbent under pads (blue pads)
- Extension set tubing
- 18-gauge stainless steel needles
- Sharps container
- Tape

Injection Supplies

- 3-mL or 5-mL polypropylene Luer lock syringe with Luer connection
- 21 gauge 1.5-inch transfer needles
- 25-gauge or 27-gauge needle for subcutaneous injection

General Supplies

- Bag-valve-mask
- Vital signs equipment
- Adverse reaction management kit
  - IV diphenhydramine,
  - IV corticosteroid (e.g., methylprednisolone 125 mg),
  - epinephrine (auto-injector preferred),
  - oxygen and delivery devices (nasal cannula and non-rebreather mask)
- Locking refrigerator with temperature monitoring capability
- Biohazard disposal bag
- Disposable disinfection wipes
- Thermometer probe covers (if required)
- 70% alcohol wipes
- Paper towels
- Trash bins and liners

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

ALS Equipment

EMS teams should carry the following additional ALS equipment for the treatment of shock:

- 0.9% NaCl for fluid bolus
- Norepinephrine
- Epinephrine

Paramedic Standing Order

Vermont EMS has expanded the Paramedic scope of practice to include administration of monoclonal antibodies with FDA approval or Emergency Use Authorization (completion of VTEMS training module required).

Monoclonal Antibodies (mAb) Administration Team

Utilize multi-disciplinary teams, when possible, for most efficient administration of mAbs, for example

- mAbs may be administered by a Paramedic, Nurse or Physician.
- AEMTs may establish IV access
- EMTs and EMRs may check vital signs and monitor patients for hypersensitivity or allergic/anaphylactic reactions.

EMS Team Configuration

- For one to three patients, the recommended crew configuration is a three-person EMS team with a minimum of one paramedic
- For four or more patients, the recommended crew configuration is a five-person EMS team with a minimum of two paramedics

When mAbs are being infused, limit the number of patient's being treated at any one time to five, unless adequate EMS staff are available to manage an adverse patient reaction in addition to patient monitoring and infusion.

EMS Team Deployment

- EMS team leads may contact local EMS resources to inquire about clinic staffing support.

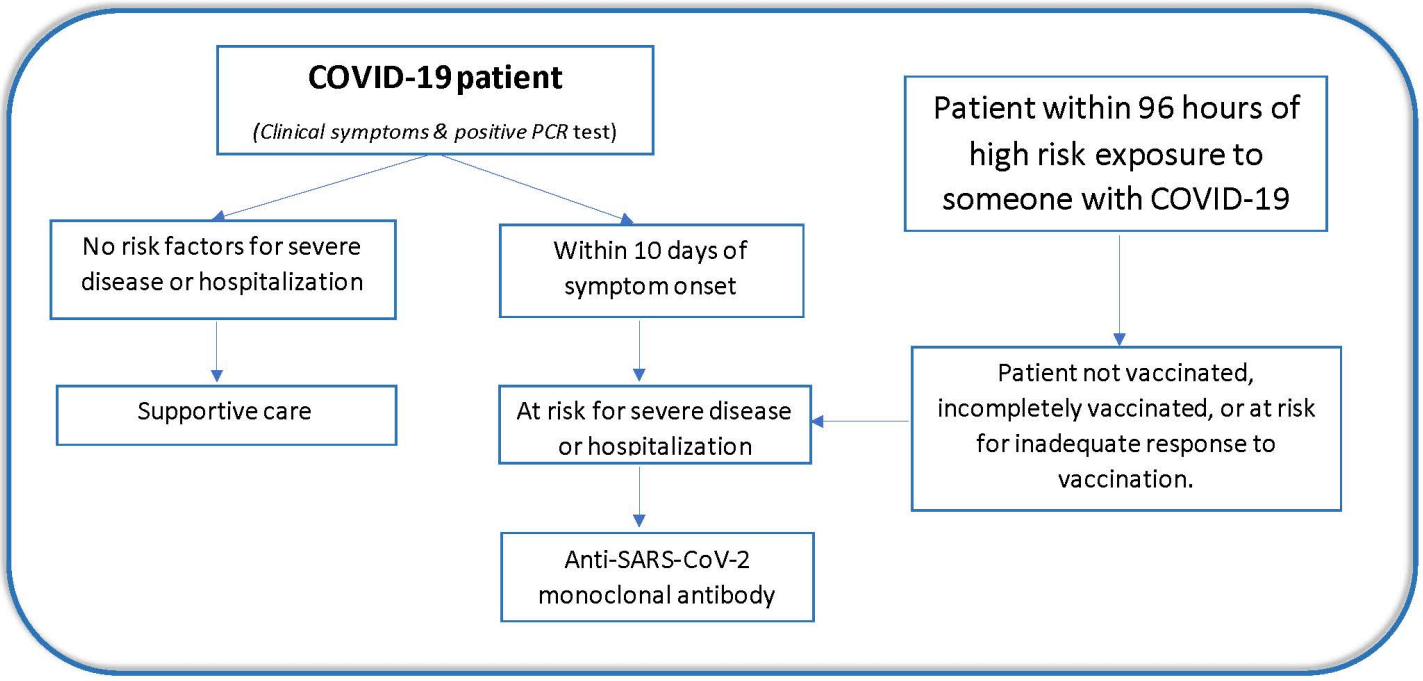
Personal Protective Equipment (PPE)

Wear full PPE while administering mAbs including face shield, gown, N95 or higher respirator that has been fit-tested, and gloves. If administering mAbs in a congregate living facility, don PPE prior to entering the facility.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Fact Sheet

- Provide a copy of the Fact Sheet for Patients, Parents, and Caregivers for RENGEN-COV (casirivimab and imdevimab) or bamlanivimab and etesevimab and explain risks, benefits and alternatives to the patient, emphasizing that this therapy is not FDA approved but is under Emergency Use Authorization (EUA).
- After reviewing the fact sheet, practitioner obtains verbal informed consent from patient, parent or caregiver.
- If the patient is unable to consent, the ordering prescriber or the facility is responsible for assuring the authorized representative has received the Fact Sheet and agrees to treatment.



Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Storage and Handling

Monoclonal antibodies are preservative-free. Discard any unused portion after use. Store unopened vials in a refrigerator at 2ºC to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE—DO NOT SHAKE—DO NOT EXPOSE TO DIRECT LIGHT OR HEAT

If given by **intravenous infusion**, solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible: store diluted solution in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) as follows:

- For **casirivimab and imdevimab (REGEN-COV)** - Store the diluted infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
- For **bamlanivimab and etesevimab** - Store the diluted infusion solution for up to 24 hours at refrigerated temperature 2°C to 8°C (36°F to 46°F) and up to 7 hours at room temperature 20°C to 25°C (68°F to 77°F) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.
- If given by **subcutaneous injection (casirivimab and imdevimab only)**, the prepared syringes should be used immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for no more than 4 hours or at room temperature up to 25ºC (77ºF) for no more than 4 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Medication Administration

Monoclonal antibodies may only be administered in settings in which health care providers have immediate access to medications to treat severe infusion or hypersensitivity reactions, such as anaphylaxis or hypotension, and the ability to activate the emergency medical system (EMS), as necessary.

Routes of Administration for REGEN-COV

- Intravenous (IV): casirivimab 600mg and imdevimab 600mg by infusion
- Subcutaneous: four subcutaneous injections given in the same visit totaling casirivimab 600mg and imdevimab 600mg.
- For treatment of symptomatic COVID-19, the intravenous route is strongly preferred under the EUA, but if there would be a delay in providing IV administration, subcutaneous administration is acceptable.
- For PEP, subcutaneous and intravenous administration are viewed clinically equivalent.

Routes of Administration for Bamlanivimab and Etesevimab

- Intravenous (IV): bamlanivimab 700 mg and etesevimab 1400 mg are added to the same infusion bag and administered together as a single intravenous infusion.
- **BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.**

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Preparation and Administration of Intravenous Infusion

Prepared infusion solution should not be administered with any other medication.

REGEN-COV (Casirivimab and imdevimab) will be prepared by placing casirivimab 600 mg and imdevimab 600 mg in a 100 mL 0.9% Sodium Chloride bag. The total volume of 110 mL is to be infused IVPB in a NS KVO primary line over **21 minutes (310 mL/hr) by IV pump**. If a pump is not available, infuse using a **10 drip set (10 drops/mL) at a rate of 53 drops/minute.**

Bamlanivimab and etesevimab will be prepared by withdrawing 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 100 mL of 0.9% Sodium Chloride. The total volume of 160 mL is to be infused IVPB in a NS KVO primary line over **31 minutes (310 mL/hr) by IV pump**. If a pump is not available, infuse using a **10 drip set (10 drops/mL) at a rate of 52 drops/minute**.

Gently invert infusion bag by hand approximately 10 times to mix. DO NOT SHAKE.

Prime the medication IV bag with a polyvinyl chloride (PVC), polyethylene (PE)-lined PVC or polyurethane (PU) infusion set containing a **0.20 or 0.22 micron filter**.

Take vital signs (VS) before start of infusion. Monitor the patient for 2-3 minutes after the start of the infusion for any signs of hypersensitivity or allergic reactions.

Follow the usual documentation requirements relevant to medication administration, patient assessments, and vital signs monitoring, including any adverse reactions.

- After infusion is complete, flush the line to ensure complete medication administration per protocol.
- Take vital signs for 60 minutes after infusion or completion of all four subcutaneous injections.
- In a group administration setting, multiple patients may be observed simultaneously by checking vital signs every 15 minutes.
- It is recommended that SARS-COV-2 vaccination be deferred for 90 days following monoclonal antibody administration.
- Patients receiving PEP should also be tested for COVID-19.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Preparation for Subcutaneous Injection

Note: Only REGEN-COV (casirivimab and imdevimab) may be administered as a 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.

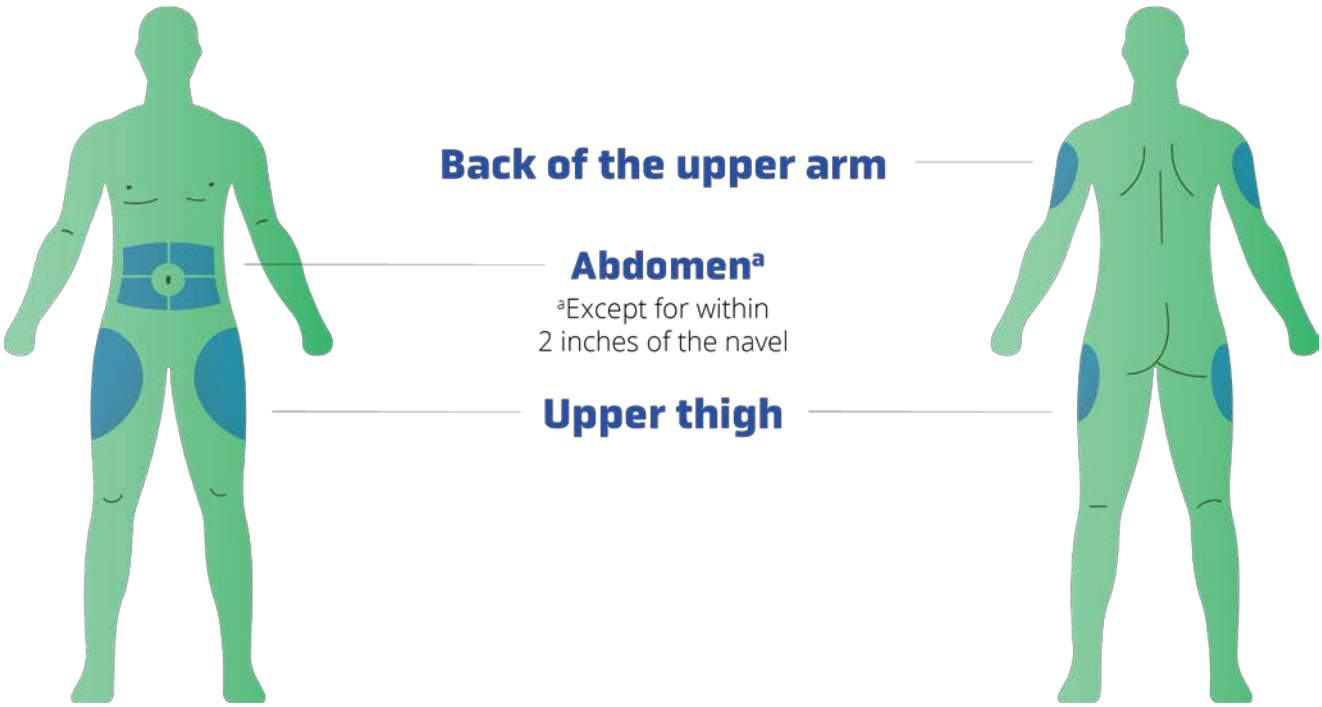
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than four hours or at 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.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Administration for Subcutaneous Injection

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

Subcutaneous Injection Sites



Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

General Guidance for Regen-Cov Dosing, Dilution, and Administration

Administration Route	Single Product Vials	REGEN-COV
Intravenous **(Mixed and administered per EUA instructions)** 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 injection or intravenous route can be used.* ★	casirivimab (REGN10933) **5ml total** (from 2.5 or 11.1 mL vials)   imdevimab (REGN10987) **5ml total** (from 2.5 or 11.1 mL vials)  	**10 mL total** 
Subcutaneous	Two syringes with 2.5 mL each of casirivimab (REGN10933) (**total of 5 ml casirivimab**) Two syringes with 2.5 mL each of imdevimab (REGN10987) (**total of 5 ml imdevimab**)	Four syringes each containing 2.5mL REGEN-COV for a **total of 10mL**

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[a]
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		

[a] 600 mg of Casirivimab and 600 mg of Imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

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

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] 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.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

General Guidance for Bamlanivimab and Etesevimab Dosing, Dilution, and Administration

1 Patient Course of
bamlanivimab/etesevimab

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a]

Drug[a]: 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		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

[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.

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Management of Adverse Reaction to Intravenous Infusion

Implement the following actions in case of hypersensitivity or allergic reactions: **NOTE: Follow Vermont Statewide EMS Protocols for Allergic Reaction/Anaphylaxis - Adult & Pediatric and/or Shock Protocol - Adult & Pediatric.**

Shortness of Breath	Tightness in the Chest	Glossal Edema
Angioedema	Periorbital or Facial Edema	Hypotension
Rash/Urticaria	Nausea/Vomiting	Tachycardia
Lightheadedness/ Dizziness	Diarrhea	

1. Stop infusion
2. Stay with patient.
3. Activate transporting EMS agency
4. Maintain patent airway and administer oxygen as needed per protocol
5. Establish IV access and initiate cardiac monitoring
6. Be prepared to administer emergency medications per VTEMS protocol
   - Epinephrine (1:1,000) **Intramuscular** Injection – 0.3mg IM or epi auto-injector
   - Benadryl IV Injection
   - Hydrocortisone, Methylprednisolone or Dexamethasone IV Injection
   - Albuterol 2.5mg nebulized or via MDI if wheezing/dyspnea
7. Obtain 12 Lead ECG if epinephrine administered
8. Treat hypotension as per VTEMS Shock Protocol
9. Initiate transport per local EMS protocol
10. Consult online Medical Direction as appropriate

Additional Resources

Fact Sheet for Health Care Providers EUA of REGEN-COV (casirivimab and imdevimab)

Fact Sheet for Health Care Providers EUA of bamlanivimab and etesevimab

REGEN-COV Dosing & Administration

Bamlanivimab and etesevimab Dosing & Administration

Federal Response to COVID-19: Monoclonal Antibody Clinical Implementation Guide

Vermont EMS Protocol for COVID-19 Monoclonal Antibody Administration

Documentation

- Prior to monoclonal antibody administration, confirm a patient-specific order from a physician or other authorized prescriber.
- Electronic Patient Care Reports must be completed in SIREN for each patient receiving administration of monoclonal antibody therapy.
- Document vital signs for 1 hour after medication administration (every 15 minutes).
- In the narrative section document the following:
    - Patient, parent or caregiver received a copy of the appropriate Fact Sheet
    - Risks, benefits and alternatives to treatment with mAbs were reviewed
    - Patient was informed that this therapy is not FDA approved but under EUA.
    - General assessment, and how the patient tolerates infusion, including potential infusion-related side effects or change in COVID-19 symptoms.
    - Lot number and expiration of the medication .
    - “mAb infused by paramedic” (if mAb given by IV infusion).
    - “mAb administered by paramedic” (if mAb given by subcutaneous injection).
- Adverse Events or death must be reported to FDA MedWatch within 7 days of event at www.fda.gov/medwatch/report.htm.
    - Submitted reports should include in the field name “Describe Event, Problem, or Product Use/ Medication Error” the statement “REGEN-COV or bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA).”
    - Serious adverse events are defined in the EUA are:
        - Death
        - Inpatient hospitalization or prolongation of existing hospitalization
        - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
        - Congenital anomaly/birth defect
        - A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly
- The prescribing healthcare provider and/or the provider’s designee are/is to provide mandatory responses to request from FDA for information about adverse events and medication errors following receipt of REGEN-COV or bamlanivimab and etesevimab.
- This protocol is based on the latest information published by the FDA, CDC, NIH, IDSA, ASPR, and ems.gov and is subject to change.