STATE OF FLORIDA
DEPARTMENT OF HEALTH
STATEWIDE STANDING ORDER FOR REGEN-COV (casirivimab and imdevimab), BAMLANIVIMAB AND ETESEVIMAB, AND SOTROVIMAB

Purpose:

This Standing Order is issued by Joseph A. Ladapo, MD, PhD, State Surgeon General, Florida Department of Health. This Standing Order authorizes registered nurses licensed under Chapter 464, Florida Statutes, and paramedics certified under Chapter 401, Florida Statutes, who are trained in the administration of monoclonal antibodies to administer REGEN-COV (casirivimab and imdevimab), bamlanivimab and etesevimab administered together, and sotrovimab:

(1) 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death; and

(2) to administer REGEN-COV (casirivimab and imdevimab) or bamlanivimab and etesevimab administered together for post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death,

in accordance with the Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) for REGEN-COV (casirivimab and imdevimab),[1] bamlanivimab and etesevimab administered together,[2] and sotrovimab[3] as updated, the Public Readiness and Emergency Preparedness Act (PREP Act) and the conditions of this order.

Standing Order Authorization:

This Standing Order is issued pursuant to the PREP Act and sections 20.43 and 381.0011, Florida Statutes, charging the Department of Health with implementing interventions that prevent or limit the impact or spread of diseases and health conditions and the duty to coordinate with federal, state, and local officials for the prevention and suppression of communicable diseases, illnesses, injuries, and hazards to human health.

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[1] https://www.fda.gov/media/145610/download (reissued September 9, 2021), https://www.fda.gov/media/145611/download (updated July 30, 2021)

[2] https://www.fda.gov/media/145801/download (reissued September 16, 2021), https://www.fda.gov/media/145803/download (updated September 16, 2021)

[3] https://www.fda.gov/media/149532/download (May 26, 2021), https://www.fda.gov/media/149533/download (May 26, 2021)

This Standing Order authorizes registered nurses licensed under Chapter 464, Florida Statutes, and paramedics certified under Chapter 401, Florida Statutes, who are trained in the administration of monoclonal antibodies to administer REGEN-COV (casirivimab and imdevimab), bamlanivimab and etesevimab administered together, and sotrovimab, covered medical countermeasures under the PREP Act, for the treatment of mild to moderate COVID-19 and for post-exposure prophylaxis (only REGEN-COV (casirivimab and imdevimab) or bamlanivimab and etesevimab administered together) of COVID-19 to authorized individuals as set forth in the FDA's EUA for REGEN-COV (casirivimab and imdevimab), bamlanivimab and etesevimab administered together, and sotrovimab, and pursuant to the applicable State of Florida Procedure and Protocol developed by the Florida Department of Health Bureau of Preparedness and Response (the Protocol), attached hereto as **"Attachment A"** and incorporated by reference, and as may be updated from time-to-time.

Procedure for administration of monoclonal antibodies by registered nurses and paramedics:

1. Verify that the individual meets the FDA EUA criteria for administration of monoclonal antibodies.
2. Review and be familiar with personal protective equipment (PPE) required for providing monoclonal antibody therapy to qualifying patients, and the Fact Sheet for Health Care Providers for the EUA of the specific monoclonal antibody therapy to be administered, attached hereto as **"Attachment B"** and incorporated by reference.
3. Review and follow the "Intravenous Infusion Preparation and Administration Instructions" outlined in the applicable Protocol for qualifying patients receiving intravenous infusion.
4. Review and follow the "Subcutaneous Injection Preparation and Administration Instructions" outlined in the applicable Protocol for qualifying patients receiving subcutaneous injections.
5. Inform each patient, or parent or legal guardian if the patient is under 18 years of age or incapable of consenting, that monoclonal antibodies for the treatment of COVID-19 are not approved by the FDA but have received emergency use authorization from the FDA for (1) the treatment of mild to moderate 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death and (2) for post-exposure prophylaxis (only REGEN-COV (casirivimab and imdevimab) or bamlanivimab and etesevimab administered together) of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Provide the current EUA Fact Sheet for Patients, Parents and Caregivers for the specific monoclonal antibodies being administered, attached hereto as **"Attachment C"** and incorporated by reference, prior to administering the therapy.
6. Receive informed written consent for use of the specific monoclonal antibodies to be administered for treatment of COVID-19 or post-exposure prophylaxis from the patient, or parent or legal guardian if the patient is under 18 years of age or incapable of consenting.
7. Submit a report on all medication errors and all serious adverse events potentially related to the monoclonal antibody therapy.
8. Advise all patients, or parents or legal guardians if the patient is under 18 years of age or incapable of consenting, to continue to self-isolate and use infection control measures.

Duration of Standing Order:

This Standing Order shall remain in effect for the duration of the FDA's EUA 91 for treatment of COVID-19 and post-exposure prophylactic use of REGEN-COV (casirivimab and imdevimab), EUA 94 for treatment of COVID-19 use of bamlanivimab and etesevimab administered together, and EUA 100 for

treatment of COVID-19 of sotrovimab, and the duration of the PREP Act immunity provisions. This Standing Order shall automatically be rescinded upon the revocation of the FDA's EUA for the monoclonal antibodies approved by that EUA, or the expiration of the COVID-19 immunity protections for covered countermeasures under the PREP Act, whichever occurs first.

Executed this 22nd day of September, 2021.

Joseph A. Ladapo, MD, PhD
ME152832
State Surgeon General
Florida Department of Health

Attachment A

Florida Department of Health Bureau of Preparedness and Response

"State of Florida Procedure and Protocol"

State of Florida

REGEN-COV™

Procedure and Protocol

Florida Department of Health

Bureau of Emergency Medical Oversight

Bureau of Preparedness and Response

August 11, 2021

Patient Selection and Post-Exposure Prophylaxis

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 REGEN-COV under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions.html.
Health care providers should consider the benefit-risk for an individual patient.

Post-Exposure Prophylaxis

This protocol is for the use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

• not fully vaccinated 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 medications) and

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC) or

- who are at high risk of exposure to an individual infected with SARS-CoV2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see Limitations of Authorized Use].

Limitations of Authorized Use

- REGEN-COV (casirivimab and imdevimab) 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 relatedcomorbidity.

- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Available Dosage Forms of REGEN-COV:

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab

2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in configurations that include 2 and 8 cartons (see below)

NDC 61755-**035**-02
Combination of 2 vials
1 vial of casirivimab 11.1 mL
AND
1 vial of imdevimab 11.1 mL

NDC 61755-**036**-08
Combination of 8 vials
4 vials of casirivimab 2.5 mL
AND
4 vials of imdevimab 2.5 mL

Patient Selection Continued and Available Dose Forms

Storage and Handling

Casirivimab and Imdevimab are preservative-free. Discard any unused portion.

Store unopened vials in a refrigerator at 2 ºC to 8 ºC (36 ºF to 46 ºF) 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 casirivimab and imdevimab solution in the refrigerator at 2 ºC to 8 ºC (36 ºF to 46 ºF) 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.

If given by subcutaneous injections, 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 4 hours or at room temperature up to 25 ºC (77 ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to 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.

PPE
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 and catheters
Infusion pumps (if available)
3-mL saline syringes
Appropriately sized syringes
Alcohol wipes
2x2 gauze pads
Adhesive bandages
Occlusive dressing
Absorbent underpads (blue pads)
Extension set tubing
18-gauge stainless steel needles
Sharps Container
Tape

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

General Supplies
Infusion reaction kit
Vital signs equipment
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 disinfecting wipes
Thermometer probe covers (if required)
70% alcohol wipes
Paper towels
Trash bins and liners

Intravenous Infusion Preparation and Administration Instructions

1. Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vial(s).

2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow

3. Obtain a prefilled intravenous infusion bag containing either 50 ml, 100 ml, 150 ml, or 250 mL of 0.9% Sodium Chloride Injection.

4. Withdraw the appropriate amount of casirivimab and imdevimab from the vial(s) and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection.

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] Individual vials may be supplied in dose packs
50 mL	Add 10 mL of co-formulated casirivimab and imdevimab (one vial) into a prefilled 0.9% Sodium Chloride infusion bag and administer as instructed on the following page	**ADD:** • 5 mL of casirivimab. May use: ◦ Two vials of 2.5 mL **OR** ◦ One vial of 11.1 mL **AND** • 5 mL of imdevimab. May use: ◦ Two vials of 2.5 mL **OR** ◦ One vial of 11.1 mL and inject into a prefilled 0.9% Sodium Chloride infusion bag and administer as instructed on the following page
100 mL		
150 mL		
250 mL		

5. Gather the recommended materials for infusion:
   a. Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set containing a 0.20 micron in-line polyethersulfone (PES) filter.

6. Attach the infusion set to the IV bag and prime.
   a. Administer the infusion solution via pump or dial-a-flow per chart below
   b. Prepared infusion is not to be administered with any other drug as compatibility is unknown

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

7. Once infusion is complete, flush the infusion line to ensure delivery of the required dose.

8. Clinically monitor patients during administration and observe for at least 1 hour after infusion.
   a. Pre-administration vital signs, then every 10-minutes and at completion of infusion

Gravity Drip Rates

DRIP RATES FOR 10-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**30**	**8**
110	21	310	**52**	**13**
160	31	310	**52**	**13**
260	50	310	**52**	**13**

DRIP RATES FOR 15-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**45**	**11**
110	21	310	**78**	**19**
160	31	310	**78**	**19**
260	50	310	**78**	**19**

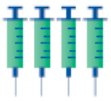
DRIP RATES FOR 20-DROPS/mL ADMINISTRATION SETS

VTBI (mL)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
60	20	180	**60**	**15**
110	21	310	**103**	**26**
160	31	310	**103**	**26**
260	50	310	**103**	**26**

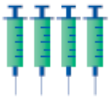
Subcutaneous Injection Preparation and Administration Instructions

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 replaced with a new vial.
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 four syringes. 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 four syringes). Prepare all four 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

Prepare 600 mg of casirivimab and 600 mg of imdevimab	Preparation of four syringes
Using casirivimab and imdevimab co-formulated vial	• Withdraw 2.5 mL solution per syringe into FOUR separate syringes
Using casirivimab and imdevimab individual vials	**Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use: • Two vials of 2.5 mL **OR** • One vial of 11.1 mL (approximately half of the vial) **AND** **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use: • Two vials of 2.5 mL **OR** • One vial of 11.1 mL (approximately half of the vial) For a total of four syringes

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

4. 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

- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5-mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred

5. Clinically monitor patients after injections and observe patients for at least 1 hour

Adverse Reactions and Reporting

Healthcare providers should direct questions about REGEN-COV (casirivimab with imdevimab) packaging or use to the Regeneron Medical Information Department at 1-844-734-6643 or to medical.information@regeneron.com.

Under the EUA, all serious adverse events and medication errors potentially related to casirivimab and imdevimab must be reported within 7 calendar days from the onset of the event. Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.

Monitor for adverse reactions (e.g. anaphylaxis) for minimum of one hour and initiate immediate treatment (below) as needed

If mild injection site reaction or allergic reaction consult ordering physician/On-Line Medical Control (OLMC) for management

If signs of severe allergic reaction/anaphylaxis (dyspnea, stridor, severe urticaria, tachycardia, hypotension, or Altered Mental Status) activate emergency response system and initiate treatment if available:

- Epinephrine 0.3 mg (1mg/mL concentration) intramuscular (may use epinephrine auto-injector if available)
- Perform Airway Management as required per local EMS protocols
- Establish IV/IO access and initiate cardiac monitoring
- Diphenhydramine 50 mg IV/IO or intramuscular
- Methylprednisolone sodium succinate 125 mg IV/IO
- Albuterol 2.5 mg nebulized if wheezing/dyspnea, may repeat x 1
- Obtain 12-lead ECG after any epinephrine administration
- Initiate transport per local EMS protocols
- Consult OLMC for additional epinephrine/epinephrine drip as needed

State of Florida Bamlanivimab and Etesevimab Procedure and Protocol

Florida Department of Health

Bureau of Emergency Medical Oversight

Bureau of Preparedness and Response

September 21, 2021

Patient Selection and Post-Exposure Prophylaxis

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 and etesevimab 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 SARSCoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 REGEN-COV under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions.html.
Health care providers should consider the benefit-risk for an individual patient.

Post-Exposure Prophylaxis

Bamlanivimab and etesevimab administered together may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for postexposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

• not fully vaccinated 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 medications) **and**

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or**

-who are at high risk of exposure to an individual infected with SARSCoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Limitations of Use:

Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19

Bamlanivimab and 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.

Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as 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.

Dosage Form of Bamlanivimab and Etesevimab:

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as soon as possible following exposure to SARS-CoV-2.

Dosage Adjustment in Specific Populations
No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation.

Storage

– If immediate administration is not possible, store the 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

Handling of Vial

– Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**. Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration. (Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.) Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into the infusion bag. Discard any product remaining in the vials. Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**

Preparation Materials

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
- Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag.

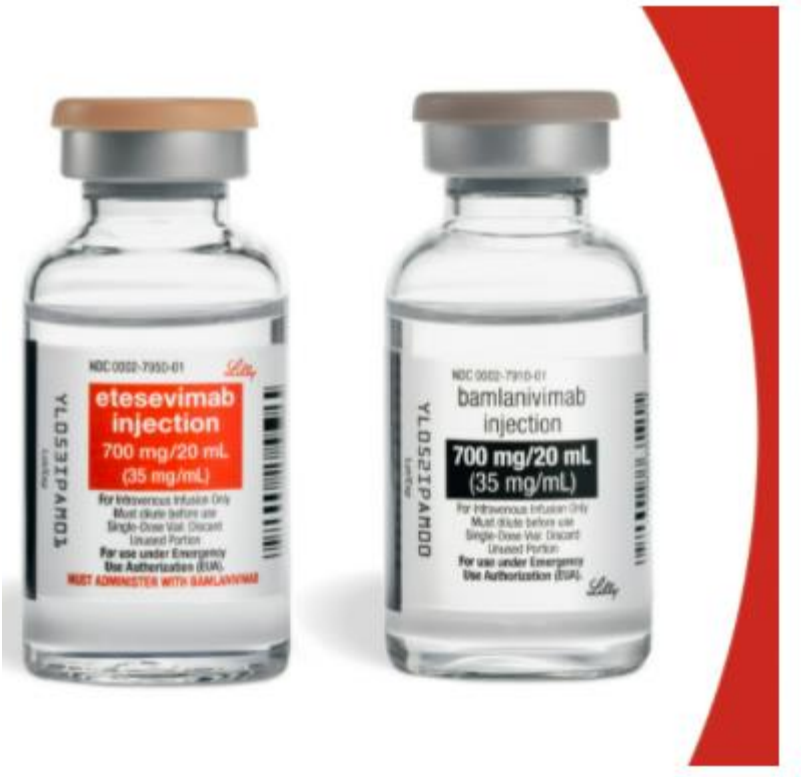
  Choose one of the following sizes:

  - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see Table 1 and Table 2 under drip rates).
- One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
- Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see Table 1 or Table 2 under drip rates).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. Do not shake.
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
- If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) 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.

Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see Table 1 under drip rates for patients weighing ≥50 kg or Table 2 for patients weighing <50 kg). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.



Drip Rates

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

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.

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

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an 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[b]	266 mL/hr	70 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.

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Adverse Reactions and Reporting

The healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to bamlanivimab and etesevimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

*Serious adverse events that must be reported to FDA MedWatch are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Submit adverse event reports to FDA MedWatch using one of the following methods:

- Complete and submit the report online at http://www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by: Mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or Call 1-800-FDA-1088 to request a reporting form.
- Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)"

Monitor for adverse reactions (e.g. anaphylaxis) for minimum of one hour and initiate immediate treatment (below) as needed

If mild injection site reaction or allergic reaction consult ordering physician/On-Line Medical Control (OLMC) for management

If signs of severe allergic reaction/anaphylaxis (dyspnea, stridor, severe urticaria, tachycardia, hypotension, or Altered Mental Status) activate emergency response system and initiate treatment if available:

- Epinephrine 0.3 mg (1mg/mL concentration) intramuscular (may use epinephrine auto-injector if available)
- Perform Airway Management as required per local EMS protocols
- Establish IV/IO access and initiate cardiac monitoring
- Diphenhydramine 50 mg IV/IO or intramuscular
- Methylprednisolone sodium succinate 125 mg IV/IO
- Albuterol 2.5 mg nebulized if wheezing/dyspnea, may repeat x 1
- Obtain 12-lead ECG after any epinephrine administration
- Initiate transport per local EMS protocols

State of Florida Sotrovimab™ Procedure and Protocol

Florida Department of Health

Bureau of Emergency Medical Oversight

Bureau of Preparedness and Response

September 10, 2021

This protocol has been authorized by the State EMS Medical Director of Florida for use during the COVID-19 Pandemic

2021

Sotrovimab Protocol Information

Patient Selection and Post-Exposure Prophylaxis

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) 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 progression to severe COVID-19, including hospitalization or death.

Sotrovimab should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 sotrovimab under the EUA 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, see https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Limitations of Authorized Use

- Sotovimab 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 relatedcomorbidity.

Patients with known hypersensitivity to any ingredient of sotrovimab must not receive sotrovimab.

Dosage Form of Sotrovimab:

The dosage of Sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single IV infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes. Sotrovimab may only be administered in settings in which healthcare 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

How supplied/dosage form and packaging

Drug Name	Sotrovimab
Strength	500 mg/8 mL (62.5 mg/mL)
Formulation	Sterile, preservative-free, clear, colorless or yellow to brown solution in a single-dose vial
Quantity	1
NDC	0173-0901-86

Sotrovimab is supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy, while lactating, or for geriatric patients. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg. See Section 11 of the Fact Sheet for Healthcare Providers.

Dose Form and Packaging

Storage Prior to Dilution

– Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

Storage After to Dilution

– The solution of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

– Sotrovimab is preservative-free. Discard unused portion.

Additional Guidance from NICA

NATIONAL INFUSION CENTER ASSOCIATION

Guidance on Medication Stability & Storage from the National Infusion Center Association[1]

Storage must not exceed 4 hours *unless* the product was prepared in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> pharmacy standards for compounding sterile products. Check with USP <797> operational considerations for sterile compounding during COVID-19 pandemic.

This is true even if storage/stability information in product labeling indicates that prepared medications may be stored for durations that exceed 4 hours.

Stability and storage duration data supplied in product labeling typically:

- Refers to chemical/physical stability rather than microbiological purity and safety, and
- Does not consider the preparation procedures used (eg, aseptic technique) or environmental conditions (eg, ISO air classification)

The longer the prepared medication is stored before administration, the more time microbial pathogens—which may be introduced via contamination during preparation—have to replicate. While the medication molecules themselves may be physically stable beyond 4 hours, the infection risk is too great.

Please visit infusioncenter.org/bestpractices for more information from NICA.

Sotrovimab Protocol Information

Preparation Instructions

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 immediate 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]).

Alteration of protein structure of monoclonal antibody medications can result from shaking or forceful aspiration or injection during preparation. Withdraw and inject Sotrovimab slowly to avoid creating turbulence or foaming.

Sotrovimab Protocol Information

Administration Instructions

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

• Gather the materials for infusion:

– Polyvinyl chloride (PVC) or polyolefin (PO) infusion set

– Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended

• Attach the infusion set to the IV bag using standard bore tubing.
• Prime the infusion set.
• Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

• Do not administer as an IV push or bolus.

• The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

• Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.

• If the infusion must be discontinued due to an infusion reaction, discard unused product.

• Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Sotrovimab requires 1 single-dose vial, 1 infusion bag, 30 minutes of infusion time, and 60 minutes of post-infusion observation.

Patients treated with Sotrovimab should continue to self-isolate and use infection control measures (eg, wear a mask, isolate, practice social distancing, avoid sharing personal items, clean and disinfect “high touch” surfaces, and wash hands frequently) according to CDC guidelines. Also see Fact Sheet for Patients, Parents, and Caregivers.

Drip Rates

Diluent Volume	Total Volume to Be Infused (VTBI)	MAXIMUM Infusion Rate	MINIMUM Infusion Time
50 mL	58 mL	100 mL/hr	34 minutes
100 mL	108 mL	200 mL/hr	32 minutes

*VTBI and minimum infusion times above differ from those provided earlier in this guide because they account for the addition of 8 mL Sotrovimab to the prefilled saline bag, resulting in a slightly larger volume and consequently a slightly longer infusion time.

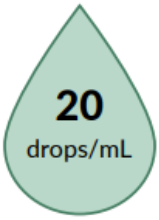
Calculating Drip Rates for Gravity Infusion

For gravity infusions, use the following formula to calculate drip rate:

$$\frac{\text{desired rate (mL/hr) X drop factor (gtts/mL)}}{\text{60 min/hr}} = \text{gtts/min}$$

Drip Rates for 10 drops/mL Admin Sets				
VTBI (ml)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
58	30	116	19	5
108	30	216	36	9

Drip Rates for 15 drops/mL Admin Sets				
VTBI (ml)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
58	30	116	29	7
108	30	216	54	14



Drip Rates for 20 drops/mL Admin Sets				
VTBI (ml)	Duration (min)	Rate (mL/hr)	Drops per minute	Drops per 15 seconds
58	30	116	39	10
108	30	216	72	18

Adverse Reactions and Reporting

The healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to Sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

*Serious adverse events that must be reported to FDA MedWatch are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Submit adverse event reports to FDA MedWatch using one of the following methods:

- Complete and submit the report online at http://www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by: Mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or Call 1-800-FDA-1088 to request a reporting form.

In addition, please provide a copy of all FDA MedWatch forms to: GlaxoSmithKline, Global Safety; Fax: 919-287-2902; Email: WW.GSKAEReportingUS@gsk.com; Or call the GSK COVID Contact Center at 1-844-GSK-COVID (844-475-2684) to report adverse events.

Monitor for adverse reactions (e.g. anaphylaxis) for minimum of one hour and initiate immediate treatment (below) as needed

If mild injection site reaction or allergic reaction consult ordering physician/On-Line Medical Control (OLMC) for management

If signs of severe allergic reaction/anaphylaxis (dyspnea, stridor, severe urticaria, tachycardia, hypotension, or Altered Mental Status) activate emergency response system and initiate treatment if available:

- Epinephrine 0.3 mg (1mg/mL concentration) intramuscular (may use epinephrine auto-injector if available)
- Perform Airway Management as required per local EMS protocols
- Establish IV/IO access and initiate cardiac monitoring
- Diphenhydramine 50 mg IV/IO or intramuscular
- Methylprednisolone sodium succinate 125 mg IV/IO
- Albuterol 2.5 mg nebulized if wheezing/dyspnea, may repeat x 1
- Obtain 12-lead ECG after any epinephrine administration
- Initiate transport per local EMS protocols

Attachment B

"Fact Sheet for Health Care Providers"

FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV™ (casirivimab and imdevimab)

AUTHORIZED USE

TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV (casirivimab and imdevimab) 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, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

POST-EXPOSURE PROPHYLAXIS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with

[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

Standing Order
Attachment B

immunocompromising conditions including those taking immunosuppressive medications[2]) **and**

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

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.

RECENT MAJOR CHANGES

- Authorized Use: addition of new indication for post-exposure prophylaxis of COVID-19 — Revised 07/2021
- Dosage and Administration (Box, and Section 2.2): updated authorized dosage for post-exposure prophylaxis of COVID-19 — Revised 07/2021
- Authorized Use: expanded the definition of progression of severe COVID-19 to include death — Revised 06/2021
- Dosage and Administration (Box, and Section 2.2): updated authorized dosage — Revised 06/2021
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with subcutaneous route of administration as an alternative for those who cannot receive intravenous infusion — Revised 06/2021

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[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

- Dosage and Administration (Box, Section 2.2 and 2.4): updated with co-formulation Revised 06/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1): addition of vasovagal reactions Revised 06/2021
- Overall Safety Summary, Clinical Trials Experience (Section 6.1): addition of Phase 3 results and safety with subcutaneous dosing Revised 06/2021
- Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (Section 18.1): addition of Phase 3 data for the authorized dose Revised 06/2021
- Dosage and Administration (Box and Section 2.1): updated high risk criteria for patient selection Revised 05/2021
- Antiviral Resistance (Box and Section 15): addition of information on susceptibility of SARS-CoV-2 variants to REGEN-COV (Table 9) Revised 03/2021
- Dose Preparation and Administration Instructions (Section 2.4): provides updated minimum infusion times based on size of infusion bag used Revised 03/2021
- New proprietary name: REGEN-COV Revised 02/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of new symptoms Revised 02/2021
- Warnings: Clinical Worsening After REGEN-COV Administration (Section 5.2) – new warning added Revised 02/2021

REGEN-COV has been authorized by FDA for the emergency uses described above.

REGEN-COV is not FDA-approved for these uses.

REGEN-COV is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGEN-COV under section 564(b)(1) of

the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Treatment

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- **not fully vaccinated[1] 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 medications[2]) and**
  - **have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[3] or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 REGEN-COV under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

SARS-CoV-2 Viral Variants

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Available Dosage Forms of REGEN-COV:

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab or
2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or in a dose pack.

Routes of Administration for REGEN-COV:

REGEN-COV may be administered by intravenous infusion or subcutaneous injection.

FOR TREATMENT, 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.

FOR POST-EXPOSURE PROPHYLAXIS, EITHER SUBCUTANEOUS INJECTION OR INTRAVENOUS INFUSION CAN BE USED.

Treatment Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- The authorized dosage of 600 mg of casirivimab and 600 mg of imdevimab for subcutaneous administration for treatment is selected based on the totality of the scientific evidence, incorporating clinical data, viral load reduction data (pharmacodynamics) and pharmacokinetic data *[see Clinical Pharmacology (14.2) and (14.3)]*.

Post-exposure Prophylaxis Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2.
- For individuals in 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.
- The authorized dosage including dosage for repeat dosing is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data *[see Clinical Trial Results and Supporting Data for EUA (18.2) and Clinical Pharmacology (14.3)]*.

For Intravenous Infusion:

- Co-formulated casirivimab and imdevimab solution in a vial and casirivimab and imdevimab solutions in individual vials must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated solution in a vial or using the individual vials (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour after injections.
- For treatment, subcutaneous injection is an alternative route of administration when intravenous administration is not feasible and would lead to delay in treatment. For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be administered.

REGEN-COV 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.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of REGEN-COV in COVID-19, please see www.clinicaltrials.gov.

Contraindications

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

Dosing

Patient Selection for Treatment and Post-Exposure Prophylaxis

This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death for:

- Treatment of mild to moderate COVID-19 in adult and pediatric patients with positive results of direct SARS-CoV-2 viral testing *[see Limitations of Authorized Use (1.1)]*.
- Post-exposure prophylaxis of COVID-19 in high risk individuals who are:
    - not fully vaccinated[1] **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 medications[2]**) and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other

individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 REGEN-COV under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

Treatment:

The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single

intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:

The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

For individuals in 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.

For Intravenous Infusion:

- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating women and in patients with renal impairment *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution containing two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials:
  - supplied in individual vials, and
  - dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, 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.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare multiple doses simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Keep any unopened vials of casirivimab and imdevimab in their original carton in the refrigerator.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

Preparation for Intravenous Infusion

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**.
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.

4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1 and Table 2).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake**.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab 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.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

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 1 vial of 11.1 mL) and • 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 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 Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Preparing Using Co-Formulated Casirivimab and Imdevimab Vial**	**Preparing Casirivimab and Imdevimab Using Individual Vials**[b]
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% sodium chloride	Add:

100 mL	infusion bag and administer as instructed below	• 2.5 mL of casirivimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of 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.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 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.

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 vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.

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 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 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	**Preparation of 4 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
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.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	**Preparation of 2 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.

Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- 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.
- 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 1 hour.

Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light.

Warnings

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a

clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life-threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- 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.

Side Effects

Adverse events have been reported with REGEN-COV (casirivimab and imdevimab) [*see Full EUA Prescribing Information, Clinical Trials Experience (6.1)*].

Additional adverse events associated with REGEN-COV, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving REGEN-COV (casirivimab and imdevimab), including:

- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate 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 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    - not fully vaccinated[1] **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 medications[2]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[3] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

- The patient or parent/caregiver has the option to accept or refuse REGEN-COV.
- The significant known and potential risks and benefits of REGEN-COV, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.

- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of REGEN-COV related to COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR REGEN-COV UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, the following items are required. Use of REGEN-COV under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate 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 viral testing and who are at high risk for severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
2. Post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    a. not fully vaccinated[1] **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 medications[2]) and
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[3] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.
3. As the health care provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving REGEN-COV. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    a. Given the "Fact Sheet for Patients, Parents and Caregivers",
    b. Informed of alternatives to receiving REGEN-COV, and
    c. Informed that REGEN-COV is an unapproved drug that is authorized for use under this Emergency Use Authorization.
4. Patients with known hypersensitivity to any ingredient of REGEN-COV must not receive REGEN-COV.

5. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to REGEN-COV treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
        - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
            - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
            - Fax (1-800-FDA-0178), or
        - Call 1-800-FDA-1088 to request a reporting form
        - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)."

    *Serious Adverse Events are defined as:
    - death;
    - a life-threatening adverse event;
    - inpatient hospitalization or prolongation of existing hospitalization;
    - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - a congenital anomaly/birth defect;
    - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6. The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of REGEN COV.

7. OTHER REPORTING REQUIREMENTS
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

    - In addition, please provide a copy of all FDA MedWatch forms to:

      Regeneron Pharmaceuticals, Inc

      Fax: 1-888-876-2736

E-mail: medical.information@regeneron.com

Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for patients who have mild to moderate COVID-19 with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

There is no adequate, approved and available alternative to REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC[3] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic.

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate 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 viral testing and who are at high risk for progression to severe COVID-19, including

hospitalization or death.[4] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, may be effective for the treatment of COVID-19 or for post-exposure prophylaxis of COVID-19 in individuals as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for REGEN-COV will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

CONTACT INFORMATION

For additional information visit www.REGENCOV.com

If you have questions, please contact Regeneron at 1-844-734-6643.

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[4] The health care provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

END SHORT VERSION FACT SHEET

Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

1.1 TREATMENT

REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the treatment of mild to moderate 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 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV (casirivimab and imdevimab) 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, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

1.2 POST-EXPOSURE PROPHYLAXIS

REGEN COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

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.

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[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

The optimal dosing regimen for treatment of COVID-19 has not yet been established.

The recommended dosing regimen may be updated as data from clinical trials become available.

Patient Selection for Treatment and Post-Exposure Prophylaxis

Treatment:

This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of adult 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis:

This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for the post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)

- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 REGEN-COV under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

Treatment:

The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Post-Exposure Prophylaxis:

The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

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.

For Intravenous Infusion:

- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

2.3 Dose Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are older than 12 years of age. REGEN-COV (casirivimab and imdevimab) is not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age *[see Use in Specific Populations (11.3)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution is available as two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials:
    - supplied in individual vials, and
    - dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, 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.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare multiple doses simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Keep any unopened vials of casirivimab and imdevimab in their original carton in the refrigerator.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

Preparation for Intravenous Infusion

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**.
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
    - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1 and Table 2).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake**.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab 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.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

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 1 vial of 11.1 mL) and
100 mL		

150 mL		• 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below
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 Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Preparing Using Co-Formulated Casirivimab and Imdevimab Vial**	**Preparing Casirivimab and Imdevimab Using Individual Vials[b]**
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 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] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, **flush the tubing** with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of 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.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time

50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 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.

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 vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
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 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 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	**Preparation of 4 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
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.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	**Preparation of 2 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- 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.
- 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 1 hour.

3 DOSAGE FORMS AND STRENGTHS

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab. Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
    - Injection: 600 mg of casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL) in a single-dose vial

2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or as dose pack.
    - Casirivimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
        - Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial
    - Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
        - Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial

- Each REGEN-COV dose pack contains 1,200 mg of casirivimab [REGN10933] and 1,200 mg of imdevimab [REGN10987] *[see How Supplied/Storage and Handling (19)]*. Casirivimab and imdevimab vial labels and carton labeling may instead be labeled REGN10933 and REGN10987, respectively.

4 CONTRAINDICATIONS

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

5.1 Hypersensitivity including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, fatigue, and diaphoresis *[see Overall Safety Summary (6.1)]*.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

5.2 Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- 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.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

Overall, approximately 16,000 subjects have been exposed to REGEN-COV (casirivimab and imdevimab) in clinical trials in hospitalized and non-hospitalized subjects. Approximately 13,500 subjects received intravenous infusions and 2,500 subjects received subcutaneous injections.

The safety of REGEN-COV (casirivimab and imdevimab) is based on analyses from COV-2067, a Phase 1/2/3 trial of ambulatory (non-hospitalized) subjects with COVID-19; COV-2069, a Phase 3 post-exposure prophylaxis trial for prevention of COVID-19; and COV-2093, a Phase 1 trial evaluating the safety and pharmacokinetics of REGEN-COV repeat subcutaneous dosing every 4 weeks for 24 weeks.

<u>COV-2067</u>

This is a randomized, double-blind, placebo-controlled clinical trial in subjects with mild to moderate COVID-19 who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. In the phase 3 portion of the trial, subjects were treated with a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=827), or 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,849), or 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=1,012), or placebo (n=1,843). REGEN-COV is not authorized at the 4,000 mg of casirivimab and 4,000 mg of

imdevimab dose. The 1,200 mg of casirivimab and 1,200 mg of imdevimab is no longer authorized under this EUA *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

In pooled phase 1/2/3 analysis, infusion-related reactions (adverse event assessed as causally related by the investigator) of grade 2 or higher severity have been observed in 10/4,206 (0.2%) of those who received REGEN-COV at the authorized dose or a higher dose *[see Warnings and Precautions (5.1)]*.

Overall, in Phase 1/2/3, three subjects receiving the 8,000 mg dose of REGEN-COV, and one subject receiving the 1,200 mg of casirivimab and 1,200 mg of imdevimab infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash) which resulted in permanent discontinuation of the infusion. All events resolved [*see Warnings and Precautions (5.1)*].

Anaphylactic reactions have been reported in the clinical program in subjects receiving REGEN-COV. The events began within 1 hour of completion of the infusion, and in at least one case required treatment including epinephrine. The events resolved.

COV-2069

This is a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2. Subjects who were SARS-CoV-2 negative at baseline were enrolled in Cohort A and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=1,311) or placebo (n=1,306).

Adverse events were reported in 265 subjects (20%) in the REGEN-COV group and 379 subjects (29%) in the placebo group. Injection site reactions (all grade 1 and 2) occurred in 55 subjects (4%) in the REGEN-COV group and 19 subjects (2%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGEN-COV group were erythema and pruritus. Hypersensitivity reactions occurred in 2 subjects (0.2%) in the REGEN-COV group and all hypersensitivity reactions were grade 1 in severity. There were no cases of anaphylaxis.

Subjects who were SARS-CoV-2 positive at baseline were enrolled in Cohort B and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=155) or placebo (n=156).

Adverse events were reported in 52 subjects (34%) in the REGEN-COV group and 75 subjects (48%) in the placebo group. Injection site reactions, all of which were grade 1 or 2, occurred in 6 subjects (4%) in the REGEN-COV group and 1 subject (1%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGN-COV group were ecchymosis and erythema. There were no cases of hypersensitivity reaction or anaphylaxis.

COV-2093

This is a randomized double-blind, placebo-controlled Phase 1 trial evaluating the safety, pharmacokinetic and immunogenicity of repeated doses of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously in healthy adult subjects. In COV-2093, subjects were randomized 3:1 to REGEN-COV (n=729) or placebo (n=240) administered every 4 weeks for 24 weeks. Adverse events were reported in 380 subjects (52%) in the REGEN-COV group and 111 subjects (46%) in the placebo group. Injection site reactions occurred in 12% and 4% of subjects following single dose administration in the REGEN-COV and placebo groups, respectively; the remaining safety findings following subcutaneous administration in the REGEN-COV group were similar to the safety findings observed with intravenous administration of REGEN-COV in COV-2067.

With repeat dosing, injection site reactions occurred in 252 subjects (35%) in the REGEN-COV group and 38 subjects (16%) in the placebo group; all injection site reactions were grade 1 or 2 in severity. Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group; and all hypersensitivity reactions were grade 1 or 2 in severity. There were no cases of anaphylaxis.

The authorized dosage for repeat dosing for post-exposure prophylaxis of COVID-19 for certain individuals who remain at high risk of exposure for longer than 4 weeks is the initial dose of 600 mg casirivimab and 600 mg imdevimab followed by 300 mg of casirivimab and 300 mg of imdevimab administered every 4 weeks *[see Dosage and Administration (2.2)]*.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete *[see Warnings and Precautions (5.1) and Clinical Trials Experience (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of REGEN-COV (casirivimab and imdevimab) are ongoing *[see Overall Safety Summary (6)]*.

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during REGEN-COV use and considered to be potentially related to REGEN-COV is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;

- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of REGEN-COV, the prescribing health care provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
    - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
    - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of REGEN-COV
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth or age
3. In section B, box 5, description of the event:
    a. Write "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
    b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:

a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report
b. Provide the address of the treating institution (NOT the health care provider's office address).

9 OTHER REPORTING REQUIREMENTS

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

In addition, please provide a copy of all FDA MedWatch forms to:

Regeneron Pharmaceuticals, Inc

Fax: 1-888-876-2736

E-mail: medical.information@regeneron.com

Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

10 DRUG INTERACTIONS

REGEN-COV consists of 2 monoclonal antibodies (mAbs), casirivimab and imdevimab, which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV (casirivimab and imdevimab) should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the

potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV (casirivimab and imdevimab) and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

REGEN-COV is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of casirivimab and imdevimab are being assessed in pediatric and adolescent patients in an ongoing clinical trial. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in Trials COV-2067, COV-2069, and COV-2093.

11.4 Geriatric Use

Of the 4,567 subjects with SARS-CoV-2 infection randomized in Trial COV-2067, 14% were 65 years or older, and 4% were 75 years of age or older. Of the 3,029 subjects randomized in Trial COV-2069, 9% were 65 years or older and 2% were 75 years of age or older. Of the 974 subjects randomized in Trial COV-2093, 13% were 65 years or older and 2% were 75 years of age or older. The difference in pharmacokinetics (PK) of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.

11.5 Renal Impairment

Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.

11.6 Hepatic Impairment

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.

11.7 Other Specific Populations

The effect of other covariates (e.g., sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.

12 OVERDOSAGE

Doses up to 8,000 mg (4,000 mg each of casirivimab and imdevimab, greater than 3 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with REGEN-COV (casirivimab and imdevimab).

13 PRODUCT DESCRIPTION

Casirivimab, a human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb), is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 145.23 kDa.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a single-dose vial for intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with imdevimab. The vial stoppers are not made with natural rubber latex.

- Casirivimab: Each 2.5 mL of solution contains 300 mg of casirivimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Casirivimab: Each 11.1 mL of solution contains 1,332 mg of casirivimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

Imdevimab, a human IgG1 mAb, is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 144.14 kDa.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a single-dose vial for intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with casirivimab. The vial stoppers are not made with natural rubber latex.

- Imdevimab: Each 2.5 mL of solution contains 300 mg of imdevimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Imdevimab: Each 11.1 mL of solution contains 1,332 mg of imdevimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

REGEN-COV (casirivimab and imdevimab solution) injection is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale yellow solution, in a single-dose 10 ml vial for intravenous infusion after dilution. The vial stoppers are not made with natural rubber latex.

- Each 10 mL of solution contains 600 mg of casirivimab, 600 mg of imdevimab, L-histidine (7.4 mg), L-histidine monohydrochloride monohydrate (10.9 mg), polysorbate 80 (10.0 mg), sucrose (800 mg), and Water for Injection, USP. The pH is 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and casirivimab and imdevimab together blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively and prevents viral attachment to host cells [*see Microbiology/Resistance Information (15)*].

14.2 Pharmacodynamics

Trial COV-2067 evaluated REGEN-COV (casirivimab and imdevimab) with doses of up to 6.66 times the recommended dose (600 mg of casirivimab and 600 mg of imdevimab; 1,200 mg of casirivimab and 1,200 mg of imdevimab; 4,000 mg of casirivimab and 4,000 mg of imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was

identified for REGEN-COV at all doses, based on viral load and clinical outcomes. Similar reductions in viral load (log10 copies/mL) were observed in subjects for the (600 mg of casirivimab and 600 mg of imdevimab) intravenous and (600 mg of casirivimab and 600 mg of imdevimab) subcutaneous doses; however, only limited clinical outcome data are available for the subcutaneous route of administration for the treatment of symptomatic patients.

14.3 Pharmacokinetics

Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between (600 mg of casirivimab and 600 mg of imdevimab) to (4,000 mg of casirivimab and 4,000 mg of imdevimab) doses of REGEN-COV (casirivimab and imdevimab) following intravenous administration of single dose. A summary of PK parameters after a single (600 mg of casirivimab and 600 mg of imdevimab) intravenous dose, for each antibody is provided in Table 7.

Table 7: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Intravenous Dose of REGEN-COV in Study COV-2067

PK Parameter[1]	Casirivimab	Imdevimab
C_{eoi} (mg/L)[2]	192 (80.9)	198 (84.8)
C_{28} (mg/L)[3]	46.2 (22.3)	38.5 (19.7)

[1] Mean (SD)
[2] concentration at end of 1-hour infusion
[3] observed concentration 28 days after dosing, i.e., on day 29, as defined in the protocol

A summary of PK parameters after a single 600 mg of casirivimab and 600 mg of imdevimab subcutaneous dose is shown in Table 8.

Table 8: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Subcutaneous Dose of REGEN-COV

PK Parameter[1,5]	Casirivimab	Imdevimab
C_{max} (mg/L)	55.6 (22.2)	52.7 (22.5)

t_{max} (day)[2]	8.00 (4.00, 87.0)	7.00 (4.00, 15.0)
AUC_{0-28} (mg●day/L)	1060 (363)	950 (362)
AUC_{inf} (mg●day/L)[3]	2580 (1349)	1990 (1141)
C_{28} (mg/L)[4]	30.7 (11.9)	24.8 (9.58)
Half-life (day)	31.8 (8.35)	26.9 (6.80)

[1] Mean (SD)
[2] Median (range)
[3] Value reported for subjects with %AUC_{inf} extrapolated <20%
[4] Observed concentration 28 days after dosing, i.e., on day 29
[5] Mean (SD) concentration at 24 hours (C_{24}) of casirivimab and imdevimab in serum with 1200 SC dosing, 22.5 (11.0) mg/L and 25.0 (16.4) mg/L, respectively

For the repeat dose prophylaxis intravenous and subcutaneous regimens, population pharmacokinetic simulations predicted that trough concentrations in serum at steady-state after an initial 600 mg casirivimab and 600 mg imdevimab intravenous or subcutaneous dose followed by monthly (every 4 weeks) 300 mg casirivimab and 300 mg imdevimab intravenous or subcutaneous doses are similar to slightly higher than observed mean day 29 concentrations in serum for a single 600 mg casirivimab and 600 mg imdevimab subcutaneous dose.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of casirivimab and imdevimab is unknown. Renal impairment is not expected to impact the PK of casirivimab and imdevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of casirivimab and imdevimab.

Drug-Drug Interactions

Casirivimab and imdevimab are mAbs which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely *[see Drug Interactions (10)]*.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 37.4 pM (0.006 μg/mL), 42.1 pM (0.006 μg/mL), and 31.0 pM (0.005 μg/mL) respectively.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were assessed using Jurkat target cells expressing SARS-CoV-2 spike protein. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCC with human natural killer (NK) effector cells. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCP with human macrophages. Casirivimab, imdevimab and casirivimab and imdevimab together did not mediate complement-dependent cytotoxicity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection

The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with recombinant vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 10-fold below the respective neutralization EC_{50} values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudotyped VLP into $Fc\gamma R2^+$ Raji and $Fc\gamma R1^+/Fc\gamma R2^+$ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and 0.06%, respectively for casirivimab and imdevimab together), but not any other cell lines tested (IM9, K562, Ramos and U937 cells).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold), L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV VLP pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included

those with E406D (51-fold), V445T (107-fold), E484Q (19-fold), G485D (5-fold), G476S (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (70-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q493R (5-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 9). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K, or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 lineage (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q, as indicated above.

Table 9: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[d]
B.1.351	South Africa	Beta	K417N, E484K, N501Y[b]	no change[d]
P.1	Brazil	Gamma	K417T, E484K, N501Y[c]	no change[d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[d]
B.1.526[e]	USA (New York)	Iota	E484K	no change[d]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[d]
B.1.617.2	India	Delta	L452R+T478K	no change[d]

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.
[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.
[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F
[d] No change: ≤2-fold reduction in susceptibility.
[e] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Table 10: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together using a Plaque Reduction Assay

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	no change[b]
B.1.617.1	India	Kappa	L452R, E484Q	no change[b]

[a] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage
[b] No change: ≤2-fold reduction in susceptibility.

In a plaque reduction assay, casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta) and B.1.617.1 (Kappa) lineages (Table 10), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold) and B.1.617.1 (6-fold) variants. Note that confirmatory sequencing of each of the tested isolates has not yet been completed.

It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a pseudotyped VSV VLP neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab.

In a toxicology study in cynomolgus monkeys, casirivimab and imdevimab had no adverse effects when administered intravenously or subcutaneously. Non-adverse liver findings (minor transient increases in AST and ALT) were observed.

In tissue cross-reactivity studies with casirivimab and imdevimab using human adult and fetal tissues, no binding of clinical concern was detected.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

Casirivimab and imdevimab administered together has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of casirivimab and imdevimab together at 25 mg/kg or 150 mg/kg into rhesus macaques (n=4 for each dosing group) 1-day post infection resulted in approximately 1-2 $\log_{10}$ reductions in genomic and sub-genomic viral RNA in nasopharyngeal swabs and oral swabs at Day 4 post-challenge in most animals, and reduced lung pathology relative to placebo-treated animals. Therapeutic administration of casirivimab and imdevimab together at 5 mg/kg and 50 mg/kg doses to hamsters 1-day post infection resulted in reduced weight loss relative to placebo treated animals. In the prophylactic setting in rhesus macaques, administration of 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 demonstrated reduction in viral RNA via nasopharyngeal, oral swabs and bronchioalveolar lavage fluid, as well as a reduction in lung inflammation. In the prophylactic setting in hamsters, administration of 0.5 mg/kg, 5 mg/kg, or 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 protected against weight loss, and reduced percentage of lung area showing pneumonia pathology and severity of lung inflammation, indicative of reduced morbidity in this model. The applicability of these findings to a clinical setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Treatment of Mild to Moderate COVID-19 (COV-2067)

The data supporting this EUA are based on the analysis of Phase 1/2/3 from trial, COV-2067 (NCT04425629). This is a randomized, double-blinded, placebo-controlled clinical trial evaluating REGEN-COV (casirivimab and imdevimab) for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Cohort 1 enrolled adult subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects in the Phase 3 primary efficacy analysis met the criteria for high risk for progression to severe COVID-19, as shown in Section 2.

In the Phase 3 trial, 4,567 subjects with at least one risk factor for severe COVID-19 were randomized to a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=838), 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,529), 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=700), or placebo (n=1,500) groups. The two REGEN-COV doses at the start of Phase 3 were 4,000 mg and 1,200 mg of each component; however, based on Phase 1/2 efficacy analyses showing that the 4,000 mg and 1,200 mg doses of each component were similar, the Phase 3 portion of the protocol was amended to compare 1,200 mg dose of each component vs. placebo and 600 mg dose of each component vs. placebo. Comparisons were between subjects randomized to the specific REGEN-COV dose and subjects who were concurrently randomized to placebo.

At baseline, in all randomized subjects with at least one risk factor, the median age was 50 years (with 13% of subjects ages 65 years or older), 52% of the subjects were female, 84% were White, 36% were Hispanic or Latino, and 5% were Black or African American. In subjects with available baseline symptom data, 15% had mild symptoms, 42% had moderate, 42% had severe symptoms, and 2% reported no symptoms at baseline; the median duration of symptoms was 3 days; mean viral load was 6.2 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary endpoint was the proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through Day 29, in subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19, i.e., the modified full analysis set (mFAS). In the mFAS, events (COVID-19-related hospitalization or all-cause death through Day 29) occurred in 7 (1.0%) subjects treated with 600 mg of casirivimab and 600 mg of imdevimab compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo (p=0.0024). Events occurred in 18 (1.3%) subjects treated with 1,200 mg of casirivimab and 1,200 mg of imdevimab compared to 62 (5%) subjects concurrently randomized to placebo, demonstrating a 71% reduction compared to placebo (REGEN-COV 1% vs placebo 5%, p<0.0001). In the 1,200 mg analysis, there was 1 death each

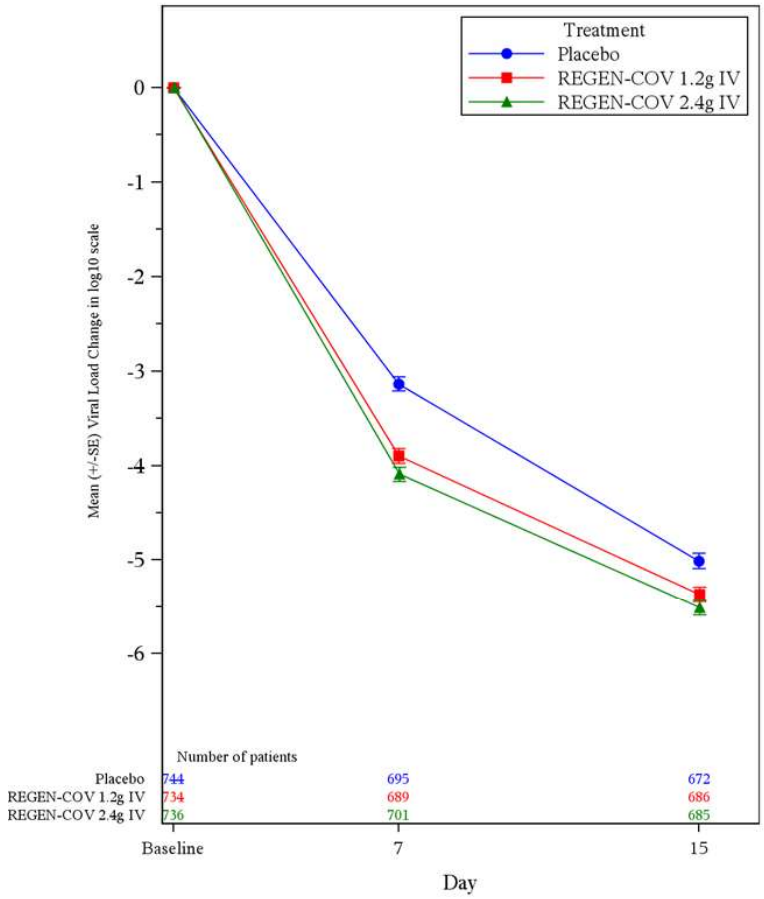
in the REGEN-COV and placebo arm (p=1.0); and in 2,400 mg analysis, there were 1 and 3 deaths, respectively, in the REGEN-COV and placebo arms (p=0.3721). Overall, similar effects were observed for 600 mg of casirivimab and 600 mg of imdevimab and 1,200 mg of casirivimab and 1,200 mg of imdevimab doses, indicating the absence of a dose effect; therefore the 600 mg of casirivimab and 600 mg of imdevimab dose is authorized and the 1,200 mg of casirivimab and 1,200 mg of imdevimab dose is no longer authorized under this EUA (See Table 11). Results were consistent across subgroups of patients defined by nasopharyngeal viral load $>10^6$ copies/mL at baseline or serologic status.

Table 11: Proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through day 29 (COV-2067)

	600 mg of casirivimab and 600 mg of imdevimab (intravenous)	**Placebo**	**1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous)**	**Placebo**
	n=736	n=748	n=1,355	n=1,341
# of subjects with at least 1 event (COVID-19-related hospitalization or all-cause death)	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	

Treatment with REGEN-COV resulted in a statistically significant reduction in the LS mean viral load (log_{10} copies/mL) from baseline to Day 7 compared to placebo (-0.71 log_{10} copies/mL for 600 mg dose of casirivimab and 600 mg of imdevimab and -0.86 log_{10} copies/mL for 2,400 mg; p<0.0001). Reductions were observed in the overall mFAS population and in other subgroups, including those with baseline viral load $>10^6$ copies/mL or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect. Figure 1 shows the mean change from baseline in SARS-COV-2 viral load to Day 15.

Figure 1: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) to Day 15 (COV-2067)



REGEN-COV 1.2 g IV = 600 mg of casirivimab and 600 mg of imdevimab administered intravenously
REGEN-COV 2.4 g IV = 1,200 mg of casirivimab and 1,200 mg of imdevimab administered intravenously

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was 10 days for REGEN-COV-treated subjects, as compared with 14 days for placebo-treated subjects ($p=0.0001$ for 600 mg of casirivimab and 600 mg of imdevimab vs. placebo; $p<0.0001$ for 1,200 mg of casirivimab and 1,200 mg of imdevimab vs. placebo). Symptoms assessed were fever, chills, sore throat, cough, shortness of breath/difficulty breathing, nausea, vomiting, diarrhea, headache, red/watery eyes, body aches, loss of taste/smell, fatigue, loss of appetite, confusion, dizziness, pressure/tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose. Time to COVID-19 symptom resolution was defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except cough, fatigue, and headache, which could have been 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

18.2 Post-exposure Prophylaxis of COVID-19 (COV-2069)

The data supporting this EUA for post-exposure prophylaxis of COVID-19 are based on the efficacy analysis of data from the Phase 3 COV-2069 trial (NCT04452318). This is a randomized, double-blind, placebo-controlled clinical trial studying REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case).

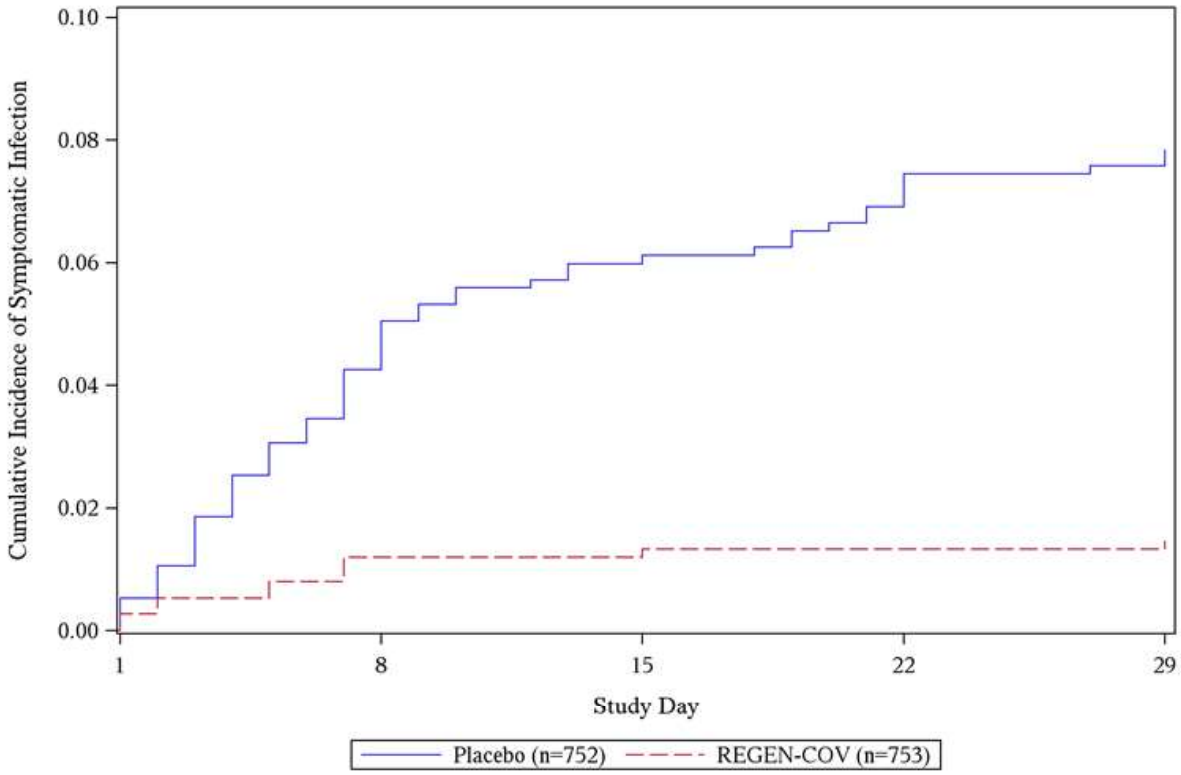
The trial enrolled subjects who were asymptomatic and who lived in the same household with a SARS-CoV-2 infected patient. Subjects were randomized 1:1 to a single dose of 600 mg of casirivimab and 600 mg of imdevimab or placebo administered subcutaneously within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.

Subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline (n=2,067) were enrolled and randomized in Cohort A. The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Of the 1,505 subjects in the primary analysis population, 753 subjects were randomized to receive REGEN-COV and 752 subjects were randomized to placebo. Following randomization and dosing, subjects had SARS-CoV-2 RT-qPCR testing via a nasopharyngeal swab every 7 days as well as weekly interviews with the investigator for assessment of COVID-19 symptoms during the 28-day efficacy assessment period. No data were collected on the type or extent of exposure to the index case.

For the primary analysis population at baseline, the median age was 44 years (with 9% of subjects ages 65 years or older), 54% of the subjects were female, 86% were White, 41% were Hispanic or Latino, and 9% were Black. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary efficacy endpoint was the proportion of subjects who developed RT qPCR-confirmed COVID-19 through Day 29. In the primary analysis population (RT-qPCR negative and seronegative at baseline), there was an 81% risk reduction in the development of COVID-19 with REGEN-COV treatment versus placebo [11/753 (1%) and 59/752 (8%); adjusted odds ratio 0.17; $p<0.0001$]. Figure 2 shows the cumulative incidence of COVID-19 through Day 29. Similar results were obtained in a sensitivity analysis that included RT-qPCR negative subjects at baseline, regardless of baseline serological status, where there was an 82% risk reduction in RT-qPCR-confirmed COVID-19 with REGEN-COV treatment versus placebo. There was a 66% risk reduction in the proportion of participants with any RT-qPCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) with REGEN-COV treatment versus placebo [36/753 (5%) and 107/752 (14%); adjusted odds ratio 0.31; $p<0.0001$].

Figure 2: Cumulative Incidence of Symptomatic COVID-19 (COV-2069 Cohort A)



In a post-hoc analysis in the subgroup of subjects who met the criteria for high risk for progression to severe COVID-19 (as shown in Section 2), there was a 76% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [10/570 (2%) vs 42/567 (7%); adjusted odds ratio 0.22; p<0.0001].

In Cohort B, asymptomatic subjects with a positive SARS-CoV-2 RT-qPCR test result at baseline (n=311) were enrolled and randomized 1:1 to REGEN-COV or placebo. In a post-hoc analysis of the overall combined Cohort A and Cohort B (regardless of serology status at baseline), there was a 62% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [46/1201 (4%) vs 119/1177 (10%); adjusted odds ratio 0.35; p<0.0001].

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Co-formulated casirivimab and imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose vial. Refer to Table 12.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose vial. Refer to Table 13.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose vial. Refer to Table 13.

REGEN-COV (casirivimab and imdevimab) injection is available as:

1. **A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab.**
2. **Individual antibody solutions in separate vials, which may be supplied in separate cartons or in a dose pack.**

Table 12: Co-Formulated Casirivimab and Imdevimab

Antibody	Concentration	Package Size	NDC Number
REGEN-COV (casirivimab and imdevimab)	600 mg/600 mg per 10 mL (60 mg/60 mg per mL)	1 vial per carton	61755-039-01

INDIVIDUAL CASIRIVIMAB AND IMDEVIMAB SOLUTIONS MUST BE ADMINISTERED TOGETHER.

Table 13: Individual Package Size

Antibody	Concentration	Package Size	NDC Number
Casirivimab REGN10933	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-024-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-026-01
Imdevimab REGN10987	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-025-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-027-01

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab [REGN10933] and imdevimab [REGN10987] to prepare up to two treatment doses (600 mg of casirivimab and 600 mg of imdevimab). Refer to Table 14.

Table 14: Dose Pack Providing 1,200 mg Casirivimab and 1,200 mg Imdevimab

Dose Pack Size	Dose Pack Components	Concentration	Dose Pack NDC Number

2 Cartons	**1 casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-035-02
	1 imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	
8 Cartons	**4 casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-036-08
	4 imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**1 casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-037-05
	4 imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**4 casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-038-05
	1 imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	

Storage and Handling
Casirivimab is preservative-free. Discard any unused portion.
Imdevimab is preservative-free. Discard any unused portion.

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

DO NOT FREEZE. DO NOT SHAKE. DO NOT EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 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 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with REGEN-COV (casirivimab and imdevimab) should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit www.REGENCOV.com

If you have questions, please contact Regeneron at 1-844-734-6643.

REGENERON

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Revised: 07/2021

FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB

AUTHORIZED USE

TREATMENT

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 and etesevimab 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 progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab

- 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%.[1]
    - 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

Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19

- Bamlanivimab and 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.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as 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.

[1] FDA will make this determination considering current variant frequency data (available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

POST-EXPOSURE PROPHYLAXIS

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 and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Limitations of Authorized Use

- 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%.[4]
    - 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
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

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[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

[4] FDA will make this determination considering current variant frequency data (available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

RECENT MAJOR CHANGES

• Authorized Use (Box and Section 1) – addition of new indication for post-exposure prophylaxis of COVID-19.	Revised 09/2021
• Clinical Trial Results and Supporting Data for EUA, Post-Exposure Prophylaxis of COVID-19 (BLAZE-2) (Section 18.2) – addition of Phase 3 data for the authorized use.	Revised 09/2021
• Authorized Use (Box and Section 1) – expanded the definition of progression of severe COVID-19 to include death.	Revised 08/2021
• Limitations of Authorized Use (Box and Section 1) – change to authorized use related to the combined frequency of SARS-CoV-2 variants that are resistant to bamlanivimab and etesevimab.	Revised 08/2021
• Antiviral Resistance (Box and Section 15) – addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab (Table 3 and Table 4) and updates based on latest viral surveillance report and additional sequencing data from Phase 3 study PYAB.	Revised 08/2021, 05/2021, and 03/2021
• Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of vasovagal reactions.	Revised 08/2021
• Warnings: Clinical Worsening After Bamlanivimab and Etesevimab Administration (Section 5.2) – updated to include administration with both antibodies.	Revised 08/2021
• Definition of High Risk for Disease Progression (Box and Section 2.1) – definition has been expanded to include additional medical conditions and other factors.	Revised 05/2021
• Dosage and Administration, Dosage (Section 2.2) – removal of rationale for authorized dose because Phase 3 data have confirmed the authorized dose.	Revised 05/2021
• Overall Safety Summary, Clinical Trials Experience (Section 6.1) – updated to integrated clinical trial safety analyses focused on adverse reactions and most common treatment-emergent adverse events.	Revised 05/2021
• Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (BLAZE-1) (Section 18.1) – addition of Phase 3 data for the authorized dose.	Revised 05/2021

Bamlanivimab and etesevimab have been authorized by FDA for the emergency uses described above.

Bamlanivimab and etesevimab are not FDA-approved for these uses.

Bamlanivimab and etesevimab are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bamlanivimab and etesevimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Treatment

This EUA is for the use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis

This EUA is for the use of the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- **not fully vaccinated[1] 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 medications[2]) and**
  - **have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] or**
  - **who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.**

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)

- 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 bamlanivimab and etesevimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

SARS-CoV-2 Viral Variants

- Review travel and contact history within 2 weeks prior to infection or exposure to SARS-CoV-2. Persons who have traveled to, resided in, or had close contact with an infected individual from an area where the frequency of resistant variants to bamlanivimab and etesevimab exceeds 5% should not receive bamlanivimab and etesevimab. Other monoclonal antibody therapy options should be considered.
- There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against the circulating variants in their state, territory, or US jurisdiction.
- Healthcare providers should also refer to Section 15 of this Fact Sheet for further details regarding specific variants and resistance.

Under this EUA, bamlanivimab and etesevimab must be administered together after dilution by intravenous (IV) infusion only.

Treatment Dosage

- The authorized dosage is 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within ten days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]*.

[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

Post-Exposure Prophylaxis Dosage

- The authorized dosage is 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after exposure to SARS-CoV-2.
- The authorized dosage is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data *[see Clinical Pharmacology (14.2) and Clinical Trial Results and Supporting Data for EUA (18.2)]*.
- The clinical data for post-exposure prophylaxis is based on data generated in the Phase 3 study BLAZE-2. While this study only evaluated dosing with bamlanivimab alone, it is reasonable to expect that bamlanivimab and etesevimab together may be safe and effective for post-exposure prophylaxis based on:
    - Phase 3 data from BLAZE-1 demonstrated treatment of COVID-19 with bamlanivimab and etesevimab together showed a statistically significant reduction in progression of severe COVID-19, including hospitalization or death *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.
    - Nonclinical and clinical data support that bamlanivimab and etesevimab together will provide an advantage over bamlanivimab alone against certain SARS-CoV-2 viral variants *[see Microbiology/Resistance Information (15)]*.
- Use of bamlanivimab and etesevimab together for post-exposure prophylaxis in subjects who meet high-risk criteria is based on a subgroup analysis of high-risk individuals enrolled in BLAZE-2 *[see Clinical Trial Results and Supporting Data for EUA (18.2)]*.

Intravenous Infusion:

- Bamlanivimab and etesevimab are both available as solutions in separate vials and must be diluted and combined prior to administration.
- To prepare the dose you will need 1 vial of bamlanivimab and 2 vials of etesevimab.
- Administer bamlanivimab and etesevimab together as a single intravenous (IV) infusion via pump or gravity (see **Table 1** and **Table 2**).
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Bamlanivimab and 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.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to bamlanivimab and etesevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

Patients treated with bamlanivimab and etesevimab together should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance,

avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of bamlanivimab and etesevimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications
None.

Dosing

BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.

Patient Selection for Treatment and Post-Exposure Prophylaxis
This section provides essential information on the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death for:

- Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing *[see Limitations of Authorized Use (1.1)]*.
- Post-exposure prophylaxis of COVID-19 in high risk individuals who are:
    - not fully vaccinated[1] **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 medications[2]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.
[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.
[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 bamlanivimab and etesevimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

Treatment:

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:

The dosage in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as soon as possible following exposure to SARS-CoV-2.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) 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.

Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

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

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.

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

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an 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[b]	266 mL/hr	70 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.

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Storage
Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze, shake, or expose to direct light.

Warnings
There are limited clinical data available for bamlanivimab and etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with use of bamlanivimab and etesevimab together.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of bamlanivimab and etesevimab under Emergency Use Authorization.

Clinical Worsening After Bamlanivimab and Etesevimab Administration
Clinical worsening of COVID-19 after administration of bamlanivimab and etesevimab together has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab and etesevimab use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19
Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as 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. Therefore, bamlanivimab and etesevimab are not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- 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.

Side Effects
Adverse events have been reported with bamlanivimab and etesevimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*.

Additional adverse events associated with bamlanivimab and etesevimab, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS
As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving bamlanivimab and etesevimab, including:

- FDA has authorized the emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
- FDA has authorized the emergency use of bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    - not fully vaccinated[1] **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 medications[2]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

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[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.
[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.
[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

- The patient or parent/caregiver has the option to accept or refuse bamlanivimab and etesevimab.
- The significant known and potential risks and benefits of bamlanivimab and etesevimab, and the extent to which such potential risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with bamlanivimab and etesevimab together should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of bamlanivimab and etesevimab together for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR BAMLANIVIMAB AND ETESEVIMAB ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:
In order to mitigate the risks of using these unapproved products and to optimize the potential benefit of bamlanivimab and etesevimab under this EUA, the following items are required. Use of bamlanivimab and etesevimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
2. Post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    a. not fully vaccinated[1] **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 medications[2]) **and**
        i. have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
        ii. who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in

[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.
[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.
[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

3. As the healthcare provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving bamlanivimab and etesevimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
   a. Given the "Fact Sheet for Patients, Parents and Caregivers",
   b. Informed of alternatives to receiving authorized bamlanivimab and etesevimab, and
   c. Informed that bamlanivimab and etesevimab are unapproved drugs that are authorized for use under this Emergency Use Authorization.
4. Patients with known hypersensitivity to any ingredient of bamlanivimab or etesevimab must not receive bamlanivimab and etesevimab.
5. The prescribing health care provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to bamlanivimab and etesevimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

   - Submit adverse event reports to FDA MedWatch using one of the following methods:
     - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
     - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
       - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
       - Fax (1-800-FDA-0178), or
     - Call 1-800-FDA-1088 to request a reporting form.
     - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)"

   *Serious Adverse Events are defined as:
   - death;
   - a life-threatening adverse event;
   - inpatient hospitalization or prolongation of existing hospitalization;
   - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
   - a congenital anomaly/birth defect;
   - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.
6. The prescribing health care provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about

adverse events and medication errors following receipt of bamlanivimab and etesevimab.

7. OTHER REPORTING REQUIREMENTS
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

    - In addition, please provide a copy of all FDA MedWatch forms to:
      Eli Lilly and Company, Global Patient Safety
      Fax: 1-317-277-0853
      E-mail: mailindata_gsmtindy@lilly.com
      Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

There is no adequate, approved and available alternative to bamlanivimab and etesevimab administered together for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

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[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

Additional information on COVID-19 therapies can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. FDA has issued this EUA, requested by Eli Lilly and Company for the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate 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 progression to severe COVID-19, including hospitalization or death.[1]

FDA has also issued this EUA, requested by Eli Lilly and Company for the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **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 medications[3]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that bamlanivimab and etesevimab

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[1] The health care provider should visit clinicaltrials.gov to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

[2] 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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[3] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[4] 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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

administered together may be effective for the treatment of mild to moderate COVID-19 or for post-exposure prophylaxis of COVID-19 in individuals as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for bamlanivimab and etesevimab will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

CONTACT INFORMATION
For additional information visit
www.LillyAntibody.com

If you have questions, please contact
1-855-LillyC19 (1-855-545-5921)

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

1.1 TREATMENT

Bamlanivimab and etesevimab administered together are authorized for use under an EUA 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 progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab

- 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%.[1]

[1] FDA will make this determination considering current variant frequency data (available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html), trends in variant

- A list of states, territories, and other 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

Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19

- Bamlanivimab and 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.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as 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 *[see Warnings and Precautions (5.3)]*.

1.2 POST-EXPOSURE PROPHYLAXIS

Bamlanivimab and etesevimab administered together are authorized for use under an EUA for post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age or older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **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 medications[2]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

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frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

[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 website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[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: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.

Limitations of Authorized Use

- 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%.[1]
    - A list of states, territories, and other 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
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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

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[1] FDA will make this determination considering current variant frequency data (available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

bamlanivimab and etesevimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

Treatment:
The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as a single intravenous infusion. Bamlanivimab and etesevimab should be given together as soon as possible following exposure to SARS-CoV-2.

Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation
No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use
No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Bamlanivimab and etesevimab are not authorized for patients weighing less than 40 kg or those less than 12 years of age *[see Use in Specific Populations (11.3)]*.

Geriatric Use
No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (11.4)]*.

Renal Impairment
No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (11.6)]*.

2.4 Dose Preparation and Administration

Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-line PVC, sterile infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) 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.

Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

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

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.

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

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[b]	266 mL/hr	70 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.

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Storage
This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Bamlanivimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) as in a single-dose vial.

Etesevimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for bamlanivimab and etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with use of bamlanivimab and etesevimab together.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of bamlanivimab and etesevimab under Emergency Use Authorization.

5.2 Clinical Worsening After Bamlanivimab and Etesevimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab and etesevimab together has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab and etesevimab use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such 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. Therefore, bamlanivimab and etesevimab are not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- 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.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The safety of bamlanivimab administered with etesevimab is primarily based on exposure of approximately 1,400 ambulatory (non-hospitalized) subjects who received doses of bamlanivimab and etesevimab together, at the recommended dose or higher, in BLAZE-1 and BLAZE-4. BLAZE-1 is a Phase 2/3, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19. In the Phase 3 portion of the trial, enrolled participants had at least one risk factor for the development of severe COVID-19 illness. BLAZE-4 is a Phase 2, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab for the treatment of subjects with mild to moderate COVID-19. Subjects ≥65 years old or with BMI ≥35 were excluded from enrollment. In clinical trials, approximately 4,000 subjects have received bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects in clinical trials *[see Clinical Pharmacology (14.2)]*.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bamlanivimab and etesevimab together at the authorized dose or higher *[see Warnings and Precautions (5.1)]*:

- anaphylaxis (n=1, 0.07%)
- infusion-related reactions (n=16, 1.1%)

In the case of anaphylaxis and serious infusion-related reactions, all infusions were stopped, and treatment was administered. One case required epinephrine. All events resolved.

The most common treatment-emergent adverse events in the bamlanivimab and etesevimab treatment group in BLAZE-1 and BLAZE-4 included nausea, dizziness, and pruritus. No treatment-emergent adverse events occurred in more than 1% of participants and the rates were comparable in the treatment and placebo groups.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete *[see Warnings and Precautions (5.1) and Overall Safety Summary (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of bamlanivimab and etesevimab are ongoing *[see Overall Safety Summary (6)]*.

Completion of FDA MedWatch Form to report all medication errors and serious adverse events* occurring during bamlanivimab and etesevimab use and considered to be potentially related to bamlanivimab and etesevimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious adverse events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of bamlanivimab and etesevimab under this EUA, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
    - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
    - Fax (1-800-FDA- 0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding adverse events and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of bamlanivimab and etesevimab
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth
3. In section B, box 5, description of the event:
    a. Write "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
    b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
    a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

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

- In addition, please provide a copy of all FDA MedWatch forms to:
  Eli Lilly and Company, Global Patient Safety
  Fax: 1-317-277-0853
  E-mail: mailindata_gsmtindy@lilly.com
  Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

10 DRUG INTERACTIONS

Bamlanivimab and etesevimab are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally

excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab and etesevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with bamlanivimab or etesevimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for etesevimab or bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab and etesevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab or etesevimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of bamlanivimab or etesevimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and etesevimab and any potential adverse effects on the breastfed child from bamlanivimab and etesevimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

Bamlanivimab and etesevimab are not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bamlanivimab and etesevimab administered together are being assessed in adolescent patients in ongoing clinical trials. The PK of bamlanivimab 700 mg and etesevimab 1,400 mg has been evaluated in pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma exposures in these 10 patients are comparable to what has been observed in adult patients at the authorized dose. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

11.4 Geriatric Use

Of the 1141 patients receiving bamlanivimab and etesevimab in BLAZE-1, 30% were 65 years of age and older and 10% were 75 years of age and older. Based on population PK analyses, there is no difference in PK of bamlanivimab or etesevimab in geriatric patients compared to younger patients *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.

11.5 Renal Impairment

Bamlanivimab and etesevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab or etesevimab.

11.6 Hepatic Impairment

Based on population PK analysis, there is no difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment.

11.7 Other Specific Populations

Based on population PK analysis, the PK of bamlanivimab and etesevimab was not affected by sex, race, or disease severity. Body weight had no clinically relevant effect on the PK of bamlanivimab and etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg.

12 OVERDOSAGE

Doses up to 7,000 mg of bamlanivimab (10 times the authorized dose of bamlanivimab) or 7,000 mg of etesevimab (5 times the authorized dose of etesevimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bamlanivimab and etesevimab should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with either bamlanivimab or etesevimab.

13 DESCRIPTION

Bamlanivimab
Bamlanivimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 146 kDa.

Bamlanivimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of bamlanivimab, and L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bamlanivimab solution has a pH range of 5.5-6.5.

Etesevimab

Etesevimab is a human IgG1 variant monoclonal antibody (mAb) consisting of 2 identical light chain polypeptides composed of 216 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 145 kDa.

Etesevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of etesevimab, L-histidine (1.55 mg), L-histidine hydrochloride monohydrate (2.10 mg), sucrose (80.4 mg), polysorbate 80 (0.5 mg), and Water for injection. The etesevimab solution has a pH range of 5.5.-6.5.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Bamlanivimab is a recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bamlanivimab binds the spike protein with a dissociation constant K_D = 0.071 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.17 nM (0.025 µg/mL).

Etesevimab is a recombinant neutralizing human IgG1κ mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Etesevimab binds the spike protein with a dissociation constant K_D = 6.45 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.32 nM (0.046 µg/mL).

Bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Using both antibodies together is expected to reduce the risk of viral resistance.

14.2 Pharmacodynamics

A flat exposure-response relationship for efficacy was identified for bamlanivimab and etesevimab administered together within the dose range of 700 mg bamlanivimab and 1,400 mg etesevimab to 2,800 mg bamlanivimab and 2,800 mg etesevimab (4 and 2 times the authorized dose, respectively), based on clinical data and pharmacokinetic/pharmacodynamic modeling.

For post-exposure prophylaxis of COVID-19, a dose of 700 mg bamlanivimab and 1,400 mg etesevimab was supported based on clinical data and pharmacokinetic/pharmacodynamic modeling.

14.3 Pharmacokinetics

Pharmacokinetic profiles of bamlanivimab and etesevimab are linear and dose-proportional between 700 mg and 7000 mg following a single IV administration. There were no differences in PK of bamlanivimab between severe/moderate participants who were hospitalized and mild/moderate ambulatory participants. There were no differences

in PK of etesevimab between mild/moderate ambulatory participants and healthy participants. There is no change in PK of bamlanivimab or etesevimab administered alone or together suggesting there is no interaction between the two antibodies.

Absorption
The mean maximum concentration (Cmax) of 700 mg bamlanivimab was 196 µg/mL (90% CI: 102 to 378 µg/mL) following approximately 1 hour 700 mg IV infusion.

The mean maximum concentration (Cmax) of 1400 mg etesevimab is estimated to be 504 µg/mL (90% CI: 262 to 974 µg/mL) following approximately 1 hour IV infusion.

Distribution
Bamlanivimab mean volume of distribution (V) was 2.87 L and 2.71 L for the central and peripheral compartments, respectively. The between subject variability was 23.2% CV.

Etesevimab mean volume of distribution (V) was 2.38 L and 1.98 L for the central and peripheral compartments, respectively. The between subject variability was 27.8% CV.

Metabolism
Bamlanivimab and etesevimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination
Bamlanivimab clearance (CL) was 0.27 L/day (between subject variability 22.3% CV) and the mean apparent terminal elimination half-life was 17.6 days (between subject variability 15.8% CV). Following a single 700 mg IV dose, bamlanivimab was quantifiable for at least 29 days. The mean concentration was 22 µg/mL (90% CI: 10.7 to 41.6 µg/mL) on Day 29.

Etesevimab clearance (CL) was 0.128 L/day (between subject variability 33.8% CV) and the mean apparent terminal elimination half-life was 25.1 days (between subject variability 29.2% CV). Following a single 1,400 mg IV dose, etesevimab was quantifiable for at least 29 days. The mean concentration was 111 µg/mL (90% CI: 57.4 to 199 µg/mL) on Day 29.

Special Populations:
The PK profiles of bamlanivimab and etesevimab were not affected by age, sex, race, or disease severity based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab or etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg *[see Use in Specific Populations (11.4, 11.7)]*.

Pediatric population
The PK of bamlanivimab and etesevimab at the authorized dose has been evaluated in 10 pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma exposures in these patients are comparable to what has been observed in adult patients. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

Patients with renal impairment
Bamlanivimab and etesevimab are not eliminated intact in the urine. Renal impairment is not expected to impact the PK of bamlanivimab and etesevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bamlanivimab and etesevimab *[see Use in Specific Populations (11.5)]*.

Patients with hepatic impairment
Based on population PK analysis, there is no significant difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (11.6)]*.

Drug interactions:
Bamlanivimab and etesevimab are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity
The cell culture neutralization activity of bamlanivimab and of etesevimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bamlanivimab, etesevimab and a 1:1 (weight/weight) ratio of bamlanivimab and etesevimab together neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with estimated EC_{50} values = 0.14 nM (0.02 µg/mL), 0.97 nM (0.14 µg/mL) and 0.14 nM (0.02 µg/mL), respectively.

Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity on reporter Jurkat cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bamlanivimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Etesevimab did not demonstrate detectable antibody-dependent cell-mediated cytotoxicity on Jurkat reporter cells expressing FcγRIIIa. Etesevimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection
The risk that bamlanivimab and etesevimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. In general, experiments with bamlanivimab, with etesevimab, and with bamlanivimab and etesevimab together did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb(s) down to at least 100-fold below the respective EC_{50} value(s).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab (Table 3).[1] There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against circulating variants in their state, territory, or US jurisdiction. Variant frequency data for states, territories, and US jurisdictions can be accessed on the following CDC website: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html.

Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T/Y. Neutralization assays using SARS-CoV-2 and vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with variant SARS-CoV-2 spike protein confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the E484D and Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484D, E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 145-fold, 24-fold, 17-fold, and 1,054-fold, respectively in a pseudotyped VLP assay.

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudotyped VLP evaluation of amino acid substitutions identified in global surveillance showed that the V483A substitution reduced susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.

Bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (Alpha; UK origin) virus and related pseudotyped VLPs expressing the spike protein found in the B.1.1.7 variant (Tables 3 and 4). SARS-CoV-2 B.1.351 lineage (Beta; South Africa origin) virus and related pseudotyped VLPs expressing spike proteins from B.1.351 lineage or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of >324, 431-fold or >45-fold, respectively. Pseudotyped VLPs expressing spike protein from the P.1 lineage (Gamma; Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of 252-fold or >3,351-fold, respectively.

Bamlanivimab and etesevimab together and etesevimab alone retained activity against SARS-CoV-2 B.1.617.2 lineage (Delta; India origin) virus and related pseudotyped

[1] 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.

VLPs, but bamlanivimab alone had reduced activity (>1,136 and >1,868-fold, respectively). Bamlanivimab and etesevimab are expected to retain activity against B.1.617.2 sublineage AY.3 (India origin). B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin) have an additional K417N substitution; pseudotyped VLPs expressing AY.1/AY.2 related spike sequence had a reduced susceptibility to bamlanivimab and etesevimab together of 1,235-fold. SARS-CoV-2 recombinant virus containing the L452R substitution present in B.1.427/B.1.429 lineages (Epsilon; USA [California] origin) and pseudotyped VLPs expressing the full-length spike protein or the L452R substitution found in this lineage showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold, 9-fold or 5-fold, respectively. Pseudotyped VLPs expressing spike protein from the B.1.617.1 lineage (Kappa; India origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 6-fold; for this variant, susceptibility to etesevimab alone was maintained, but not to bamlanivimab alone (>1,030-fold reduction). Bamlanivimab and etesevimab together and etesevimab alone retained activity against pseudotyped VLPs expressing the full-length spike protein from the C.37 lineage (Lambda; Peru origin), but bamlanivimab alone had reduced activity (>2,112-fold reduction). Pseudotyped VLPs expressing spike protein from the B.1.621 lineage (Mu; Colombia origin) show reduced susceptibility to bamlanivimab and etesevimab together of 116-fold, due to susceptibility reductions to bamlanivimab (>1,863-fold) and etesevimab (17-fold) alone.

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

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	431[c]
P.1	Brazil	Gamma	K417T + E484K + N501Y	252[c]
B.1.617.2/AY.3	India	Delta	L452R + T478K	no change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N][d]	L452R + T478K + K417N	1,235[c]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	9[e]
B.1.526[f]	USA (New York)	Iota	E484K	30
B.1.617.1	India	Kappa	L452R + E484Q	6[e]
C.37	Peru	Lambda	L452Q + F490S	no change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	116[c]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudoviruses containing the full-length spike protein reflective of the consensus sequence for each of the variant lineages were tested.
[b] No change: <5-fold reduction in susceptibility.
[c] Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.
[d] Commonly known as “Delta plus.”
[e] Etesevimab retains activity against this variant.
[f] 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).

Table 4: Authentic[a] SARS-CoV-2 Neutralization Data for Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	>325
B.1.617.2/AY.3	India	Delta	L452R, T478K	no change[c]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	11
B.1.526[d]	USA (New York)	Iota	E484K	11

[a] The B.1.1.7 variant was assessed using cell culture-expanded virus isolates and tested using an immunofluorescence based microneutralization assay and by plaque reduction assay; B.1.351 and B.1.617.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.526/E484K and B.1.427/B.1.429/L452R substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K or L452R) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility.

[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 recombinant SARS-CoV-2 with the E484K substitution only.

Due to the large reduction of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (Beta; South Africa origin), P.1 (Gamma; Brazil origin), AY.1/AY.2 (“Delta plus”; India origin), and B.1.621 (Mu; Colombia origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes.

In authentic SARS-CoV-2 assays, bamlanivimab and etesevimab together retained activity against variants of B.1.1.7 (Alpha) and B.1.617.2/AY.3 (Delta) lineages (Table 4), although bamlanivimab alone had reduced activity to B.1.617.2/AY.3 (Delta) in this assay (>1,136-fold). SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (Iota; USA [New York] origin) or the L452R substitution present in the B.1.427/B.1.429 lineage (Epsilon; USA [California] origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold. Susceptibility to etesevimab alone was maintained for both isolates, but not to bamlanivimab alone (>833-fold and >1,460-fold reduction for E484K and L452R viruses, respectively). Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together result in similar viral load reductions in participants infected with the L452R variant (Epsilon; USA [California] origin) as observed in those who were infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized (p=0.15).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Analysis of

baseline samples show that 8.4% (188/2246) of clinical trial patients were infected with viral variants containing single amino acid substitutions at positions associated with reduced susceptibility to either bamlanivimab or etesevimab as predicted by pseudotyped VLP or authentic SARS-CoV-2 neutralization assays. No patients were infected with a variant that was predicted to have reduced susceptibility to both bamlanivimab and etesevimab by these assessments.

Patient samples were also analyzed for treatment-emergent viral variants, defined as variants with single amino acid substitutions at positions that had reduced susceptibility to either bamlanivimab or etesevimab present at an allele fraction of ≥15%.

- In the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in 9.0% (42/467) of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in 5.3% (21/394) of patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg together, and in 4.0% (27/674) of patients treated with placebo. The majority of these were only detected at one time point in the sequential series with 0.9% (4/467), 1.0% (4/394), and 0.3% (2/674) of patients having multiple instances of detection in the bamlanivimab 2,800 mg and etesevimab 2,800 mg together, bamlanivimab 700 mg and etesevimab 1,400 mg together, and placebo groups, respectively.
- In patients treated with bamlanivimab and etesevimab together, substitutions detected in one or more patients included ones with reduced susceptibility (≥5-fold) to bamlanivimab only: L452R/W, E484K, G485V, F490L, and S494P; and ones with reduced susceptibility to etesevimab only: D405G/Y, K417N, D420N/Y, N460H/I/T, A475S/V, Y489H, and N501I/Y. While these variants had reduced susceptibility to either bamlanivimab OR etesevimab compared to wild-type in a pseudotyped VSV VLP or authentic virus assay they still retained susceptibility to the other antibody in the combination.
- There were also observations of variants with reduced susceptibility (≥5-fold) to both bamlanivimab and etesevimab and to bamlanivimab + etesevimab tested together: E484D (n=1; 145-fold reduction to bamlanivimab + etesevimab tested together at a molar ratio of 1:2), Q493K/R (n=9; 584-fold and 1,054-fold reduction to bamlanivimab + etesevimab tested together at a molar ratio of 1:2 for Q493K and Q493R, respectively) out of a total of 861 patients treated with bamlanivimab and etesevimab together.
- In a subgroup of participants infected with virus harboring L452R substitution found in the B.1.427/B.1.429 (Epsilon) lineage, a S459P treatment-emergent substitution was identified in one subject. Concurrent L452R+S459P substitutions conferred a 1,656-fold reduction in susceptibility to bamlanivimab + etesevimab together (1:2 molar ratio).
- Additional treatment-emergent substitutions in patients treated with bamlanivimab and etesevimab together, with no phenotypic data, include D405del, D420G, C480R, G485D, S494L, and P499L. The impact of these substitutions on susceptibility is not currently known.

It is possible that bamlanivimab and etesevimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation
There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bamlanivimab or etesevimab have not been conducted.

In toxicology studies, bamlanivimab and etesevimab had no adverse effects when administered intravenously to rats and monkeys, respectively. Non-adverse increases in neutrophils were observed in rats dosed with bamlanivimab.

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected for bamlanivimab or etesevimab.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

Antiviral Activity In Vivo
Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 $\log_{10}$ decreases in viral genomic RNA and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation.

Prophylactic or therapeutic administration of etesevimab to male Rhesus macaques (n=3 per group) resulted in approximately 4 or 3 $\log_{10}$ average decreases, respectively, in viral genomic RNA in oropharyngeal swabs at Day 4 post infection relative to control animals.

The applicability of these findings to a prophylaxis or treatment setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Treatment of Mild to Moderate COVID-19 (BLAZE-1)

The data supporting this EUA for treatment of mild to moderate COVID-19 are primarily based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501). This trial provides Phase 3 placebo-controlled clinical efficacy data from subjects receiving 700 mg bamlanivimab and 1,400 mg of etesevimab together, as well as for subjects receiving 2,800 mg bamlanivimab and 2,800 mg etesevimab together.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects in the Phase 3 portion of the trial met the criteria for high-risk (as defined in Section 2).

Phase 3 Data from BLAZE-1 (bamlanivimab 700 mg and etesevimab 1,400 mg)
In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg and etesevimab 1,400 mg (N=511) or placebo (N=258). The majority (99.2%) of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 were also enrolled in the trial (10 [2.0%] were treated with bamlanivimab and etesevimab and 13 [1.7%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

At baseline, median age was 56 years (with 30% of subjects aged 65 or older); 53% of subjects were female, 87% were White, 27% were Hispanic or Latino, and 8% were Black or African American. Subjects had mild (76%) to moderate (24%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 24.33 at baseline. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 15 subjects treated with placebo (6%) as compared to 4 events in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together (0.8%) [$p<0.0001$], an 87% reduction. There were 4 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together ($p=0.01$).

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 1).

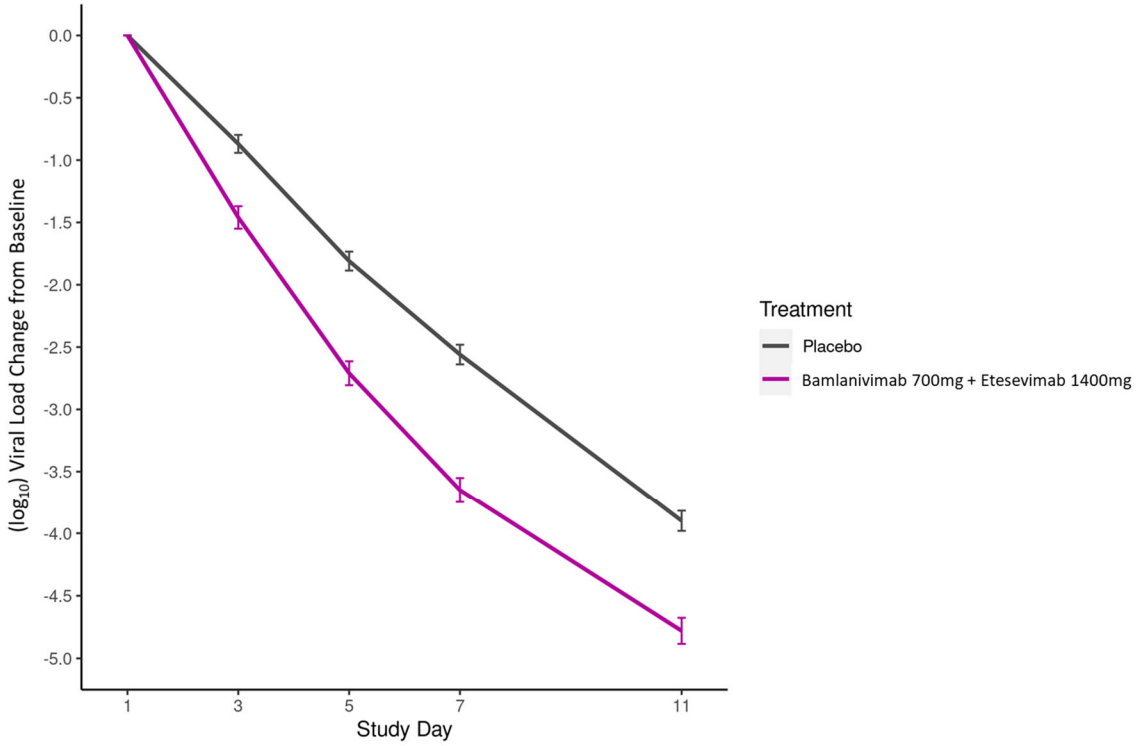


Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Phase 3 Portion of BLAZE-1 (700 mg bamlanivimab and 1,400 mg etesevimab).

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days for subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together as compared with 10 days for subjects treated with placebo (p=0.009). Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

Phase 3 Data from BLAZE-1 (bamlanivimab 2,800 mg and etesevimab 2,800 mg)
Subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=518) or placebo (N=517). All of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years of age, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 years were also enrolled in the trial (4 [0.8%] were treated with bamlanivimab and etesevimab and 7 [1.4%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

Bamlanivimab 2,800 mg and etesevimab 2,800 mg is not an authorized dosage under this EUA. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [p<0.001], a 70% reduction. There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (p<0.001).

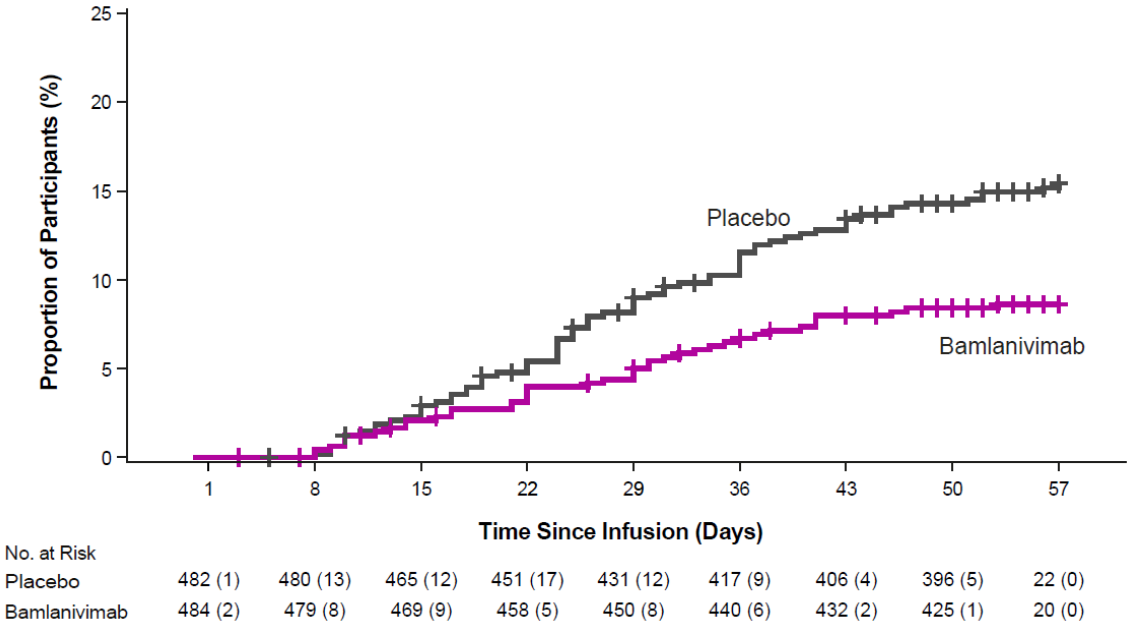
18.2 Post-Exposure Prophylaxis of COVID-19 (BLAZE-2)

The data supporting this EUA for post-exposure prophylaxis of COVID-19 are based on the final analysis of Part 1 of the Phase 3 trial BLAZE-2 (NCT04497987). The database lock occurred after all enrolled subjects completed Day 57. BLAZE-2 Part 1 is a randomized, double-blind, placebo-controlled study evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility. All participants in Part 1 were randomized and treated with a single infusion of bamlanivimab 4,200 mg or placebo. Results of baseline testing for SARS-CoV-2 were not known until after the therapy was administered. Those with a positive baseline SARS-CoV-2 RT-PCR test were included in the Treatment Population (N=132) and those with a negative test were included in the Prevention Population (N=966). Individuals in these populations were also required to have a baseline negative SARS-CoV-2 serology test; those who tested positive were only included in the overall safety population.

Data are presented for the Prevention Population only. No data were collected on the type or extent of exposure to the index case in the Prevention Population.

In the overall Prevention Population (N=484 for bamlanivimab 4,200 mg and N=482 for placebo) at baseline, the median age was 53 years (with 29% of subjects aged 65 or older); 75% of subjects were female, 89% were White, 5% were Hispanic or Latino, and 8% were Black. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups.

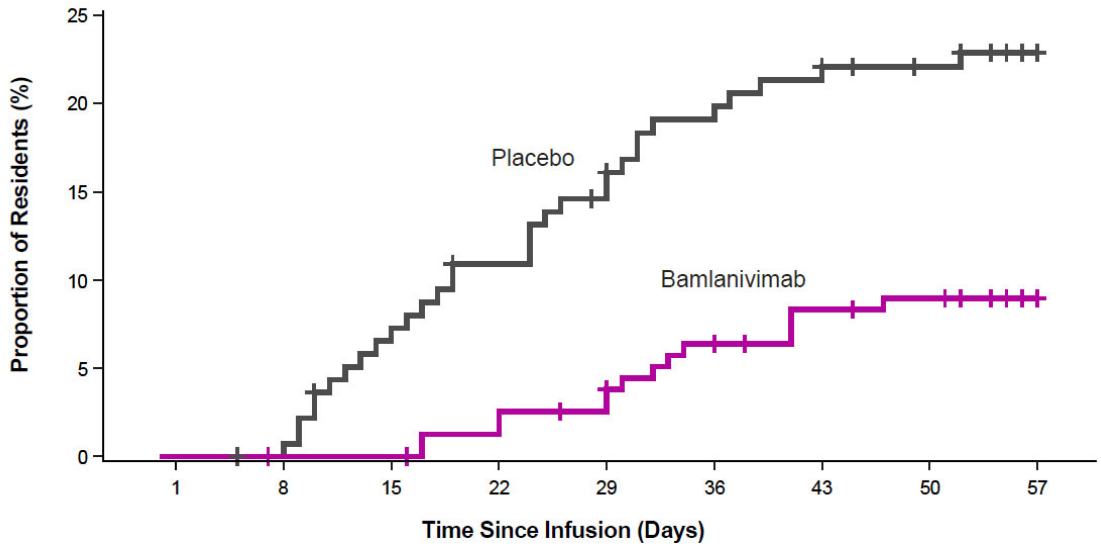
The primary endpoint (cases of symptomatic COVID-19 by Day 57) was assessed after all participants in the Prevention Population reached 8 weeks of follow-up, and analysis were adjusted for facility, sex, and role within facility (resident/staff). There were 114 cases of symptomatic COVID-19, with a lower frequency occurring in participants treated with bamlanivimab as compared to placebo (residents and staff; adjusted odds ratio 0.43; p<0.001) reducing the risk of being infected with COVID-19 by up to 57%. As a supplementary analysis, the time to symptomatic COVID-19 is shown for each arm in Figure 2. Four COVID-19-related deaths were reported in the overall Prevention Population; all occurred in the placebo arm (0.8%). No COVID-19-related deaths occurred in the bamlanivimab arm.



No. at Risk									
Placebo	482 (1)	480 (13)	465 (12)	451 (17)	431 (12)	417 (9)	406 (4)	396 (5)	22 (0)
Bamlanivimab	484 (2)	479 (8)	469 (9)	458 (5)	450 (8)	440 (6)	432 (2)	425 (1)	20 (0)

Figure 2: Time to symptomatic COVID-19 in the overall prevention population (residents and staff).

For the pre-specified subgroup of nursing home residents, there were 45 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.20; p<0.001), reducing the risk of being infected with COVID-19 by up to 80%. The time to symptomatic COVID-19 in nursing home residents is shown by treatment arm in Figure 3. In this same cohort of residents within the Prevention Population, 6 deaths due to any cause occurred in residents treated with placebo (4.3%) and 5 deaths due to any cause occurred in residents treated with bamlanivimab (3.1%).



No. at Risk									
Placebo	139 (1)	137 (9)	127 (5)	121 (7)	112 (5)	107 (3)	102 (0)	99 (1)	2 (0)
Bamlanivimab	161 (0)	159 (0)	159 (4)	154 (2)	150 (4)	145 (3)	141 (1)	139 (0)	5 (0)

Figure 3: Time to symptomatic COVID-19 in residents only.

For the post-hoc subgroup of patients who met the high risk criteria (all residents and all high risk staff[1]), there were 75 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.28; nominal p<0.001), reducing the risk of being infected with COVID-19 by up to 72%.

For the post-hoc subgroup of staff who did not meet high risk criteria, there were 39 cases of symptomatic COVID-19, with less evidence of a preventative effect for bamlanivimab versus placebo (adjusted odds ratio 0.64; nominal p=0.26).

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

UNDER THIS EUA, BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER.

Bamlanivimab
Bamlanivimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Etesevimab
Etesevimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

[1] All high risk participants in the Prevention Population were either residents in a skilled nursing or assisted living facility, or staff in a skilled nursing or assisted living facility who satisfied at least 1 of the following at the time of screening: were ≥65 years of age, had a BMI ≥35, had CKD, had diabetes, had immunosuppressive disease, were currently receiving immunosuppressive treatment, OR were ≥55 years of age AND had cardiovascular disease, OR hypertension, OR COPD or other chronic respiratory disease.

Bamlanivimab and etesevimab are supplied as:

Antibody	Concentration	Package Size	NDC
Bamlanivimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7910-01
Etesevimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7950-01

Storage and Handling
Bamlanivimab is preservative-free. Discard unused portion.
Etesevimab is preservative-free. Discard unused portion.

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

DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT.

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

20 PATIENT COUNSELING INFORMATION

Patients treated with bamlanivimab and etesevimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit:
www.LillyAntibody.com

If you have questions, please contact:
1-855-LillyC19 (1-855-545-5921)

Literature revised September 16, 2021

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ETE-0005-EUA HCP-20210916

FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sotrovimab 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 progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab 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).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Sotrovimab has been authorized by FDA for the emergency use described above.

Sotrovimab is not FDA-approved for this use.

Sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

This EUA is for the use of the unapproved product sotrovimab for the treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17 years

of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)

- 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 anomalies)
- 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 sotrovimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Sotrovimab may only be administered in settings in which healthcare 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.

Sotrovimab must be administered after dilution by intravenous (IV) infusion.

Healthcare providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to sotrovimab. See Sections 8 and 9 of the Full EUA

Prescribing Information for reporting instructions below.

- See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.
- The authorized dosage for sotrovimab is one single IV infusion of 500 mg administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18)]*.
- Sotrovimab is available as a concentrated solution and must be diluted prior to administration.
- Administer 500 mg of sotrovimab by IV infusion over 30 minutes.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of sotrovimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications

None.

Dosing

Patient Selection and Treatment Initiation

This section provides essential information on the unapproved product sotrovimab, for the treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)

- 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 anomalies)
- 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 sotrovimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

The dosage of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 500 mg of sotrovimab. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

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 of sotrovimab from one vial and inject into the 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 immediate 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

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
    - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
    - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other

medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

Warnings

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with use of sotrovimab.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in patients *[see Limitations of Authorized Use]*:

- 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).

Side Effects

Adverse events have been reported with sotrovimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*.

Additional adverse events associated with sotrovimab may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents, and Caregivers" (and provide a copy of the Fact Sheet**)** prior to the patient receiving sotrovimab, including:

- FDA has authorized the emergency use of sotrovimab for treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.
- The patient or parent/caregiver has the option to accept or refuse sotrovimab.
- The significant known and potential risks and benefits of sotrovimab and the extent to which such risks and benefits are unknown.

- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of sotrovimab for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SOTROVIMAB UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of sotrovimab, the following steps are required. Use of sotrovimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.
2. As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients, Parents, and Caregivers" prior to the patient receiving sotrovimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    a. Given the "Fact Sheet for Patients, Parents, and Caregivers",
    b. Informed of alternatives to receiving authorized sotrovimab, and
    c. Informed that sotrovimab is an unapproved drug that is authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of sotrovimab must not receive sotrovimab.
4. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.
    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online at www.fda.gov/medwatch/report.htm, or

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.
- Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)."

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

5. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.
6. OTHER REPORTING REQUIREMENTS
   - In addition, please provide a copy of all FDA MedWatch forms to:

     GlaxoSmithKline, Global Safety
     Fax: 919-287-2902
     Email: WW.GSKAEReportingUS@gsk.com

     Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to sotrovimab for the treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death. Additional information on COVID-19 treatments can be found at http://www.covid19treatmentguidelines.nih.gov/. The

healthcare provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued this EUA, as requested by GlaxoSmithKline, for the unapproved product, sotrovimab, for the treatment of mild-to-moderate 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 progression to severe COVID-19, including hospitalization or death.[1] As a healthcare provider, you must comply with the mandatory requirements of this EUA (see above).

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that sotrovimab may be effective for the treatment of mild-to-moderate COVID-19 in certain at-risk patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for sotrovimab will end when the Secretary determines that the circumstances justify the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

END SHORT VERSION FACT SHEET

Long Version Begins on Next Page

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[1] The healthcare provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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1 AUTHORIZED USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) 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 progression to severe COVID-19, including hospitalization or death *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab 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).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Authorized Use (1) and Clinical Trial Results and Supporting Data for EUA (18)]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- 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 anomalies)
- 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 sotrovimab under the EUA 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, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

The dosage of sotrovimab in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single IV infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg *[see Use in Specific Populations (11.3)]*.

Geriatric Use

No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (11.4)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

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 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 of sotrovimab from one vial and inject into the 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 immediate 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

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
  - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

This product is preservative-free; therefore, the diluted infusion solution should be administered

immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial for intravenous infusion after dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Overall Safety Summary (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use

Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in patients *[see Limitations of Authorized Use]*:

- 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.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of sotrovimab is primarily based on an interim analysis from 868 patients through Day 15 *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

All patients received a single 500-mg infusion of sotrovimab (n = 430) or placebo (n = 438). Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each.

Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a study in hospitalized patients; the infusion was immediately discontinued, and the patient received epinephrine. The event resolved but recurred within 2 hours; the patient received another dose of epinephrine and

improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in patients hospitalized due to COVID-19 *[see Warnings and Precautions (5.1, 5.3)]*.

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (2%) and diarrhea (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of sotrovimab are ongoing *[see Overall Safety Summary (6)]*.

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during sotrovimab use and considered to be potentially related to sotrovimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious adverse events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of sotrovimab, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm, or

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information should include:

- Patient demographics (e.g., patient initials, date of birth),
- Pertinent medical history,
- Pertinent details regarding admission and course of illness,
- Concomitant medications,
- Timing of adverse event(s) in relationship to administration of sotrovimab,
- Pertinent laboratory and virology information,
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Section A, Box 1, provide the patient's initials in the Patient Identifier.
2. In Section A, Box 2, provide the patient's date of birth.
3. In Section B, Box 5, description of the event:
   a. Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line.
   b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In Section G, Box 1, name and address:
   a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
   b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com
  Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

10 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab. Since sotrovimab is an Fc-enhanced human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and

any potential adverse effects on the breastfed infant from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults based on an allometric scaling approach (which accounted for effect of body weight changes associated with age on clearance and volume of distribution).

11.4 Geriatric Use

Of the 430 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 10% were over 70 years of age. The difference in pharmacokinetics (PK) of sotrovimab in geriatric patients compared to younger patients has not been quantified.

11.5 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

11.6 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

12 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

There is no specific treatment for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 PRODUCT DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for intravenous infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution

of sotrovimab has a pH of 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant (K_D = 0.21 nM) but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

14.2 Pharmacokinetics

It is expected that the half-life of sotrovimab is longer than Fc-unmodified IgG due to the LS modification, but data are not available. Based on noncompartmental analysis, the mean (geomean) C_{max} following a 1 hour IV infusion was 137 µg/mL (N = 129, CV% 40), and the mean (geomean) Day 29 concentration was 34 µg/mL (N = 78, CV% 23) from all subjects with an available Day 29 sample.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of sotrovimab is unknown. Renal impairment is not expected to impact the PK of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the PK of sotrovimab.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

The neutralization activity of sotrovimab against SARS-CoV-2 (isolate USA WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS-CoV-2 with an average EC_{50} value of 0.67 nM (100.1 ng/mL) and an average EC_{90} value of 1.2 nM (186.3 ng/mL).

Sotrovimab demonstrated cell culture FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles) and FcγRIIb. Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) in cell culture using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using $CD14^+$ monocytes targeting cells expressing spike protein.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, lung weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

An E340A amino acid substitution in the spike protein emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. A pseudotyped VLP assessment in cell culture showed that epitope amino acid sequence polymorphisms P337H/L/R/T and E340A/K/G conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: E340K (>297), P337R (>276), P337L (180), E340A (>100), E340G (27), P337H (7.5), and P337T (5.4). The presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against the UK (2.3-fold change in EC_{50} value; B.1.1.7: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), South Africa (0.6-fold change in EC_{50} value; B.1.351: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V), Brazil (0.35-fold change in EC_{50} value; P.1: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F), California (0.7-fold change in EC_{50} value; CAL.20C: S13I, W152C, L452R, D614G), New York (0.6-fold change in EC_{50} value; B.1.526: L5F, T95I, D253G, E484K, D614G, A701V), and India (0.7-fold change in EC_{50} value; B.1.617; T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H) variant spike proteins (Table 1). Microneutralization data using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the UK (3-fold change in EC_{50} value), South Africa (1.2-fold change in EC_{50} value) and Brazil (1.6-fold change in EC_{50} value) variants (Table 1).

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

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility (Pseudotyped VLP)	Fold Reduction in Susceptibility (Authentic Virus)
B.1.1.7 (UK origin)	N501Y	No change[b]	No change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	No change[b]	No change[b]
P.1 (Brazil origin)	K417T + E484K + N501Y	No change[b]	No change[b]
B.1.427/B.1.429 (California origin)	L452R	No change[b]	nd[d]
B.1.526 (New York origin)[c]	E484K	No change[b]	nd[d]
B.1.617 (India origin)	L452R + E484Q	No change[b]	nd[d]

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed.

[b] No change: <5-fold reduction in susceptibility

[c] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[d] Not determined.

Limited nucleotide sequencing data from a total of 218 participants, at the time of authorization, indicated that 9 participants (5 placebo and 4 treated with sotrovimab) enrolled in COMET-ICE were infected with the CAL.20C variant (S13I, W152C, L452R), and one subject treated with sotrovimab progressed to require hospitalization. Two additional participants in the placebo group carried the L452R variant only. None of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the UK (B.1.1.7), South African (B.1.351), or Brazilian (P.1) variants. One participant in the placebo group carried the N501Y variant at baseline.

In COMET-ICE, post-baseline epitope variants were detected in eight participants in the cohort receiving sotrovimab (spike protein substitutions E340K [4 subjects: ≥99.7% allele frequency]; A344V [6.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]). Of the variants detected at baseline and post-baseline, L335F, G339C, E340A, E340K, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold and >297-fold changes in EC_{50} value, respectively). Sotrovimab retains susceptibility against L335F (0.8-fold change in EC_{50} value), G339C (1.2-fold change in EC_{50} value), R346I (1.7-fold

change in EC_{50} value), K356N (1.1-fold change in EC_{50} value), K356R (0.8-fold change in EC_{50} value), R357I (1-fold change in EC_{50} value), I358V (0.7-fold change in EC_{50} value), and S359G (0.8-fold change in EC_{50} value) substitutions. The clinical impact of these variants is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of virus in the lung (as measured by $TCID_{50}$) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Clinical data supporting this EUA are based on an interim analysis from the Phase 1/2/3 COMET-ICE trial (NCT #04545060) that occurred after 583 randomized subjects had the opportunity to complete at least Day 29 of the trial. COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of comorbidities. The study included symptomatic patients with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of

enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised patients were excluded from the trial. Subjects were treated with a single 500-mg infusion of sotrovimab (n = 291) or placebo (n = 292) over 1 hour (Intent to Treat [ITT] population at interim analysis 1).

At baseline, the median age was 53 years (range:18 to 96); 22% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 7% Black or African American, 6% Asian, 63% Hispanic or Latino. Fifty-eight percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days. The three most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), and diabetes requiring medication (23%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo (p = 0.002). Table 2 provides the results of the primary endpoint and a key secondary endpoint of COMET-ICE.

Table 2. Interim Efficacy Results in Adults with Mild-to-Moderate COVID-19

	Sotrovimab n = 291	**Placebo n = 292**
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)		
Proportion (n, %)	3 (1%)	21 (7%)
Adjusted Relative Risk Reduction (97.24% CI)	85% (44%, 96%)	
p-value	0.002	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

Analysis of change from baseline in viral load in COMET-ICE is not yet possible because data are not available in the majority of trial participants.

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze

or shake. Protect from light.

The solution of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also, see "Fact Sheet for Patients, Parents, and Caregivers".

21 CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

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Revised: July 2021

DETACH HERE AND GIVE FACT SHEET TO PATIENT, PARENT OR CAREGIVER.

- -

FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS
Emergency Use Authorization (EUA) of Sotrovimab for the Treatment of Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called **sotrovimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking sotrovimab, which you may receive.

Receiving sotrovimab may benefit certain people with COVID-19.

Read this Fact Sheet for information about sotrovimab. Talk to your healthcare provider if you have any questions. It is your choice to receive sotrovimab or stop it at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your other medical conditions to become worse.

What is sotrovimab?
Sotrovimab is an investigational medicine used to treat mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death. Sotrovimab is investigational because it is still being studied. There is limited information about the safety and effectiveness of using sotrovimab to treat people with mild-to-moderate COVID-19.

The U.S. Food & Drug Administration (FDA) has authorized the emergency use of sotrovimab for the treatment of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

What should I tell my healthcare provider before I receive sotrovimab?
Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

How will I receive sotrovimab?

- You will receive 1 dose of sotrovimab.

- Sotrovimab will be given to you through a vein (intravenous or IV infusion) over 30 minutes.
- You will be observed by your healthcare provider for at least 1 hour after you receive sotrovimab.

What are the important possible side effects of sotrovimab?

Possible side effects of sotrovimab are:

- **Allergic reactions.** Allergic reactions can happen during and after infusion with sotrovimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever; difficulty breathing; low oxygen level in your blood; chills; tiredness; fast or slow heart rate; chest discomfort or pain; weakness; confusion; nausea; headache; shortness of breath; low or high blood pressure; wheezing; swelling of your lips, face, or throat; rash including hives; itching; muscle aches; dizziness; feeling faint; and sweating.

The side effects of getting any medicine through a vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of sotrovimab. Not many people have been given sotrovimab. Serious and unexpected side effects may happen. Sotrovimab is still being studied, so it is possible that all of the risks are not known at this time.

It is possible that sotrovimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, sotrovimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

What other treatment choices are there?

Like sotrovimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with sotrovimab. Should you decide not to receive sotrovimab, or stop it at any time, it will not change your standard medical care.

What if I am pregnant or breastfeeding?

There is no experience treating pregnant women or breastfeeding mothers with sotrovimab. For a mother and unborn baby, the benefit of receiving sotrovimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with sotrovimab?

Tell your healthcare provider right away if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088, or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

How can I learn more?

- Ask your healthcare provider
- Visit www.sotrovimabinfo.com
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Visit https://combatcovid.hhs.gov/i-have-covid-19-now/available-covid-19-treatment-options
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?

The FDA has made sotrovimab available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

Sotrovimab has not undergone the same type of review as an FDA-approved medicine. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. All of these criteria must be met to allow for the medicine to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for sotrovimab is in effect for the duration of the COVID-19 declaration justifying emergency use of these medicines, unless terminated or revoked (after which the products may no longer be used).

Manufactured by **GlaxoSmithKline LLC**
Philadelphia, PA 19112, U.S. License No. 1727
Distributed by **GlaxoSmithKline**
Research Triangle Park, NC 27709

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Attachment C

"EUA Fact Sheet for Patients, Parents and Caregivers"

FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS
EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV™
(casirivimab and imdevimab) FOR CORONAVIRUS DISEASE 2019 (COVID-19)

You are being given a medicine called **REGEN-COV (casirivimab and imdevimab)** for the treatment or post-exposure prevention of coronavirus disease 2019 (COVID-19). SARS-CoV-2 is the virus that causes COVID-19. This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking REGEN-COV.

Receiving REGEN-COV may benefit certain people with COVID-19 and may help prevent certain people who have been exposed to someone who is infected with SARS-CoV-2 from getting SARS-CoV-2 infection, or may prevent certain people who are at high risk of exposure to someone who is infected with SARS-CoV-2 from getting SARS-CoV-2 infection.

Read this Fact Sheet for information about REGEN-COV. Talk to your healthcare provider if you have questions. It is your choice to receive REGEN-COV or stop at any time.

WHAT IS COVID-19?

COVID-19 is caused by a virus called a coronavirus, SARS-CoV-2. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

WHAT ARE THE SYMPTOMS OF COVID-19?

The symptoms of COVID-19 include fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your other medical conditions to become worse.

WHAT IS REGEN-COV (casirivimab and imdevimab)?

REGEN-COV is an investigational medicine used in adults and adolescents (12 years of age and older who weigh at least 88 pounds (40 kg)) who are at high risk for severe COVID-19, including hospitalization or death for:

- treatment of mild to moderate symptoms of COVID-19
- post-exposure prevention of COVID-19 in persons who are:
    - not fully vaccinated against COVID-19 (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]), **or**,
    - are not expected to build up enough of an immune response to the complete COVID-19 vaccination (for example, someone with immunocompromising

conditions, including someone who is taking immunosuppressive medications), **and**

- have been exposed to someone who is infected with SARS-CoV-2. Close contact with someone who is infected with SARS-CoV-2 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). For additional details, go to https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html, **or**
- someone who is at high risk of being exposed to someone who is infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, as nursing homes, prisons,).

REGEN-COV is investigational because it is still being studied. There is limited information known about the safety and effectiveness of using REGEN-COV to treat people with COVID-19 or to prevent COVID-19 in people who are at high risk of being exposed to someone who is infected with SARS-CoV-2. REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

The FDA has authorized the emergency use of REGEN-COV for the treatment of COVID-19 and the post-exposure prevention of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

WHO SHOULD NOT TAKE REGEN-COV?

Do not take REGEN-COV if you have had a severe allergic reaction to REGEN-COV.

WHAT SHOULD I TELL MY HEALTH CARE PROVIDER BEFORE I RECEIVE REGEN-COV?

Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Have had a severe allergic reaction including anaphylaxis to REGEN-COV previously
- Have received a COVID-19 vaccine.
- Have any serious illnesses
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Are taking any medications (prescription, over-the-counter, vitamins, and herbal products)

HOW WILL I RECEIVE REGEN-COV (casirivimab and imdevimab)?

- REGEN-COV consists of two investigational medicines, casirivimab and imdevimab, given together at the same time through a vein (intravenous or IV) or injected in the

tissue just under the skin (subcutaneous injections). **Your healthcare provider will determine the most appropriate way for you to be given REGEN-COV.**

- Treatment: If you are receiving an intravenous infusion, the infusion will take 20 to 50 minutes or longer. Your healthcare provider will determine the duration of your infusion.
    - If your healthcare provider determines that you are unable to receive REGEN-COV as an intravenous infusion which would lead to a delay in treatment, then as an alternative, REGEN-COV can be given in the form of subcutaneous injections. If you are receiving subcutaneous injections, your dose will be provided as multiple injections given in separate locations around the same time.
- Post-exposure prevention: If you are receiving subcutaneous injections, your dose will be provided as multiple injections given in separate locations around the same time. If you are receiving an intravenous infusion, the infusion will take 20 to 50 minutes or longer.
    - After the initial dose, if your healthcare provider determines that you need to receive additional doses of REGEN-COV for ongoing protection, the additional intravenous or subcutaneous doses would be administered monthly.

WHAT ARE THE IMPORTANT POSSIBLE SIDE EFFECTS OF REGEN-COV (casirivimab and imdevimab)?

Possible side effects of REGEN-COV are:

- Allergic reactions. Allergic reactions can happen during and after infusion or injection of REGEN-COV. Tell your healthcare provider right away or seek immediate medical attention if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, feeling faint, dizziness and sweating. These reactions may be severe or life threatening.
- Worsening symptoms after treatment: You may experience new or worsening symptoms after infusion or injection, including fever, difficulty breathing, rapid or slow heart rate, tiredness, weakness or confusion. If these symptoms occur, contact your healthcare provider or seek immediate medical attention as some of these symptoms have required hospitalization. It is unknown if these symptoms are related to treatment or are due to the progression of COVID-19.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site. The side effects of getting any medicine by subcutaneous injection may include pain, bruising of the skin, soreness, swelling, and possible infection at the injection site.

These are not all the possible side effects of REGEN-COV. Not a lot of people have been given REGEN-COV. Serious and unexpected side effects may happen. REGEN-COV is still being studied so it is possible that all of the risks are not known at this time.

It is possible that REGEN-COV could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, REGEN-COV may reduce your body’s immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

WHAT OTHER TREATMENT CHOICES ARE THERE?
Like REGEN-COV (casirivimab and imdevimab), FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by FDA that are used to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

It is your choice to be treated or not to be treated with REGEN-COV. Should you decide not to receive REGEN-COV or stop it at any time, it will not change your standard medical care.

WHAT OTHER PREVENTION CHOICES ARE THERE?
Vaccines to prevent COVID-19 are also available under Emergency Use Authorization. Use of REGEN-COV does not replace vaccination against COVID-19. REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

WHAT IF I AM PREGNANT OR BREASTFEEDING?
There is limited experience using REGEN-COV (casirivimab and imdevimab) in pregnant women or breastfeeding mothers. For a mother and unborn baby, the benefit of receiving REGEN-COV may be greater than the risk of using the product. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

HOW DO I REPORT SIDE EFFECTS WITH REGEN-COV (casirivimab and imdevimab)?
Tell your healthcare provider right away if you have any side effect that bothers you or does not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 or call 1-844-734-6643.

HOW CAN I LEARN MORE?
- Ask your health care provider.
- Visit www.REGENCOV.com
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Contact your local or state public health department.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?
The United States FDA has made REGEN-COV (casirivimab and imdevimab) available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

REGEN-COV has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. All of these criteria must be met to allow for the medicine to be used in the treatment of COVID-19 or prevention of COVID-19 during the COVID-19 pandemic.

The EUA for REGEN-COV is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

REGENERON

Manufactured by:
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Revised: 07/2021

Fact Sheet for Patients, Parents and Caregivers
Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab for Coronavirus Disease 2019 (COVID-19)

You are being given two medicines together called **bamlanivimab and etesevimab** for the treatment or post-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19). SARS-CoV-2 is the virus that causes COVID-19. This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking bamlanivimab and etesevimab.

Receiving bamlanivimab and etesevimab may help to treat COVID-19 in certain people, or help to prevent COVID-19 in certain people who have been exposed to someone infected with SARS-CoV-2 or who are at high risk of an exposure because of where they live, such as nursing homes or prisons.

Read this Fact Sheet for information about bamlanivimab and etesevimab. Talk to your healthcare provider if you have questions. It is your choice to receive bamlanivimab and etesevimab or stop them at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus, SARS-CoV-2. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 include fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your other medical conditions to become worse.

What are bamlanivimab and etesevimab?
Bamlanivimab and etesevimab are investigational medicines used together in adults and adolescents (12 years of age and older who weigh at least 88 pounds (40 kg)) who are at high risk for developing severe COVID-19, including hospitalization or death for:

- **treatment** of mild to moderate symptoms of COVID-19, OR

- **post-exposure prophylaxis for prevention** of COVID-19 in persons who are:
    - not fully vaccinated against COVID-19 (Individuals are considered to be fully vaccinated 2 weeks after their second dose in a 2-dose series [such as the Pfizer or Moderna vaccines], or 2 weeks after a single-dose dose vaccine [such as Johnson & Johnson's Janssen vaccine]), **or**
    - are not expected to build up enough of an immune response to the complete COVID-19 vaccination (for example, someone with immunocompromising conditions, including someone who is taking immunosuppressive medications), **and**
        - have been exposed to someone who is infected with SARS-CoV-2. Close contact with someone who is infected with SARS-CoV-2 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). For additional details, go to https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html, **or**

- someone who is at high risk of being exposed to someone who is infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Bamlanivimab and etesevimab are investigational because they are still being studied. There is limited information known about the safety or effectiveness of using bamlanivimab and etesevimab to treatment or prevention of COVID-19. Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

The FDA has authorized the emergency use of bamlanivimab and etesevimab together for the treatment of COVID-19 and the post-exposure prophylaxis for prevention of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the section "**What is an Emergency Use Authorization (EUA)?**" at the end of this Fact Sheet.

What should I tell my healthcare provider before I receive bamlanivimab and etesevimab?
Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Have received a COVID-19 vaccine
- Have any serious illnesses
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Are taking any medications (prescription, over-the-counter, vitamins, and herbal products)

How will I receive bamlanivimab and etesevimab?

- Bamlanivimab and etesevimab are given to you at the same time through a vein (intravenous or IV).
- You will receive one dose of bamlanivimab and etesevimab by IV infusion. The infusion will take 21 – 60 minutes or longer. Your healthcare provider will determine the duration of your infusion.

What are the important possible side effects of bamlanivimab and etesevimab?

Possible side effects of bamlanivimab and etesevimab are:

- Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab and etesevimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, feeling faint, dizziness, and sweating. These reactions may be severe or life threatening.
- Worsening of COVID-19 symptoms after bamlanivimab and etesevimab therapy for active infection: You may experience new or worsening symptoms after infusion for mild to moderate COVID-19, including fever, difficulty breathing, rapid or slow heart rate, tiredness, weakness or confusion. If these occur, contact your healthcare provider or seek immediate medical attention as some of these events have required hospitalization. It is unknown if these events are related to treatment or are due to the progression of COVID-19.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of bamlanivimab and etesevimab. Not a lot of people have been given bamlanivimab and etesevimab. Serious and unexpected side effects may happen. Bamlanivimab and etesevimab are still being studied so it is possible that all of the risks are not known at this time.

It is possible that bamlanivimab and etesevimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bamlanivimab and etesevimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

What other treatment choices are there?
Like bamlanivimab and etesevimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

It is your choice to be treated or not to be treated with bamlanivimab and etesevimab. Should you decide not to receive bamlanivimab and etesevimab or stop it at any time, it will not change your standard medical care.

What other prevention choices are there?
Vaccines to prevent COVID-19 are approved or available under Emergency Use Authorization. Use of bamlanivimab and etesevimab does not replace vaccination against COVID-19.

Like bamlanivimab and etesevimab, FDA may allow for the emergency use of other medicines for post-exposure prophylaxis for prevention of COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by FDA for post-exposure prophylaxis for prevention of COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

What if I am pregnant or breastfeeding?
There is limited experience treating pregnant women or breastfeeding mothers with bamlanivimab and etesevimab. For a mother and unborn baby, the benefit of receiving bamlanivimab and etesevimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with bamlanivimab and etesevimab?
Tell your healthcare provider right away if you have any side effect that bothers you or does not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch, call 1-800-FDA-1088, or contact Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921).

How can I learn more?
- Ask your healthcare provider
- Visit www.LillyAntibody.com
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?
The United States FDA has made bamlanivimab and etesevimab available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

Bamlanivimab and etesevimab have not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. All of these criteria must be met to allow for the medicine to be used in the treatment of COVID-19 or prevention of COVID-19 during the COVID-19 pandemic.

The EUA for bamlanivimab and etesevimab together is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

Literature revised September 16, 2021

Eli Lilly and Company, Indianapolis, IN 46285, USA

ETE-0004-EUA PAT-20210916

FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS
Emergency Use Authorization (EUA) of Sotrovimab for the Treatment of Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called **sotrovimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking sotrovimab, which you may receive.

Receiving sotrovimab may benefit certain people with COVID-19.

Read this Fact Sheet for information about sotrovimab. Talk to your healthcare provider if you have any questions. It is your choice to receive sotrovimab or stop it at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?

The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your other medical conditions to become worse.

What is sotrovimab?

Sotrovimab is an investigational medicine used to treat mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death. Sotrovimab is investigational because it is still being studied. There is limited information about the safety and effectiveness of using sotrovimab to treat people with mild-to-moderate COVID-19.

The U.S. Food & Drug Administration (FDA) has authorized the emergency use of sotrovimab for the treatment of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

What should I tell my healthcare provider before I receive sotrovimab?
Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

How will I receive sotrovimab?

- You will receive 1 dose of sotrovimab.
- Sotrovimab will be given to you through a vein (intravenous or IV infusion) over 30 minutes.
- You will be observed by your healthcare provider for at least 1 hour after you receive sotrovimab.

What are the important possible side effects of sotrovimab?

Possible side effects of sotrovimab are:

- **Allergic reactions.** Allergic reactions can happen during and after infusion with sotrovimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever; difficulty breathing; low oxygen level in your blood; chills; tiredness; fast or slow heart rate; chest discomfort or pain; weakness; confusion; nausea; headache; shortness of breath; low or high blood pressure; wheezing; swelling of your lips, face, or throat; rash including hives; itching; muscle aches; dizziness; feeling faint; and sweating.

The side effects of getting any medicine through a vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of sotrovimab. Not many people have been given sotrovimab. Serious and unexpected side effects may happen. Sotrovimab is still being studied, so it is possible that all of the risks are not known at this time.

It is possible that sotrovimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, sotrovimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

What other treatment choices are there?

Like sotrovimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with sotrovimab. Should you decide not to receive sotrovimab, or stop it at any time, it will not change your standard medical care.

What if I am pregnant or breastfeeding?

There is no experience treating pregnant women or breastfeeding mothers with sotrovimab. For a mother and unborn baby, the benefit of receiving sotrovimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with sotrovimab?

Tell your healthcare provider right away if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088, or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

How can I learn more?

- Ask your healthcare provider
- Visit www.sotrovimabinfo.com
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Visit https://combatcovid.hhs.gov/i-have-covid-19-now/available-covid-19-treatment-options
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?

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Manufactured by **GlaxoSmithKline LLC**
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Research Triangle Park, NC 27709

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