AUTHORIZED USE AND IMPORTANT SAFETY INFORMATION

REGEN-COV, (casirivimab with imdevimab to be administered together) is authorized for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. [see Limitations of Authorized Use]

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA
- This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner
- Healthcare providers should review the **Fact Sheet for Healthcare Providers** for information on the authorized use of REGEN-COV and mandatory requirements of the EUA and must comply with the requirements of the EUA. The **FDA Letter of Authorization** is available for reference, as well as the **Dear Healthcare Provider Letter** and **Patient Fact Sheet**

LIMITATIONS OF AUTHORIZED USE

- REGEN-COV (casirivimab with 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
- Benefit of treatment with REGEN-COV has not been observed in patients hospitalized due to 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

DEFINITION OF HIGH RISK PATIENTS

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12–17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
  - sickle cell disease, OR
  - congenital or acquired heart disease, OR
  - neurodevelopmental disorders, for example, cerebral palsy, OR
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control

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 the **Fact Sheet for Healthcare Providers** for details regarding specific variants and resistance, and refer to the **CDC website** as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Refer to the **Fact Sheet for Healthcare Providers** and visit **regencov.com** for more information.
Please see **Important Safety Information** below.

DOSAGE AND DILUTION INSTRUCTIONS FOR REGEN-COV

CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.

REGEN-COV Dose Packs containing sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare **one treatment dose** are now available. Please be sure not to mix any dose-pack vials that you may receive with single-carton vials of casirivimab and imdevimab, which are still in distribution.

PREPARATION INSTRUCTIONS

Casirivimab and imdevimab are each supplied in individual single-dose vials. Casirivimab with imdevimab infusion solution must be diluted prior to administration.

Casirivimab with imdevimab solution for 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 solution must be discarded, and fresh solution prepared.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow
3. Obtain a prefilled IV infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial* using 2 separate syringes (see **Table 2**) and inject all 20 mL into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1**). Discard any product remaining in the vial.
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.
   - 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[†]

Each REGEN-COV Dose Pack contains sufficient number of vials of casirivimab and imdevimab to prepare one treatment dose. Vials should remain in the dose pack until time of preparation of the IV solution. See **Table 2.**

*Multiple vials may be needed to obtain 10 mL. See preparation and administration instructions on page 3.

[†]These times were based on preparation in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> Pharmaceutical Compounding–Sterile Preparations.

Table 1: Recommended Dosing, Dilution and Administration Instructions for Casirivimab with Imdevimab for IV Infusion

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	210 mL/hr	20 minutes
100 mL	310 mL/hr	23 minutes
150 mL	310 mL/hr	33 minutes
250 mL	310 mL/hr	52 minutes

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

1,200 mg casirivimab and 1,200 mg imdevimab are added to the same infusion bag and administered together as a single IV infusion. After infusion is complete, flush with 0.9% Sodium Chloride Injection.

Refer to the **Fact Sheet for Healthcare Providers** and visit **regencov.com** for more information.
Please see **Important Safety Information** below.

PREPARATION INSTRUCTIONS (CONT'D)

Table 2: Casirivimab with Imdevimab for Intravenous (IV) Infusion (to be administered together as a 2,400-mg dose)[a]

Antibody dose	Volume to withdraw from vial(s)	Number of vials needed[b]
Casirivimab REGN10933 1,200 mg	10 mL	1 vial of 11.1 mL **OR** 4 vials of 2.5 mL
Imdevimab REGN10987 1,200 mg	10 mL	1 vial of 11.1 mL **OR** 4 vials of 2.5 mL

[a]1,200 mg of casirivimab and 1,200 mg of imdevimab are added to the same infusion bag and administered together as a single IV infusion.
[b]One 11.1-mL vial of one antibody may be prepared with four 2.5-mL vials of the other antibody to create one treatment course.

ADDITIONAL INFORMATION FOR HEALTHCARE PROVIDERS:

- Casirivimab and imdevimab are each provided in a separate carton and vial. **Casirivimab** and **imdevimab** vial labels and carton labeling may instead be labeled **REGN10933** and **REGN10987**, respectively
- Each REGEN-COV dose pack contains sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose
- You may receive cartons and vials of casirivimab and imdevimab that are labeled "for intravenous infusion or subcutaneous injection." **However, casirivimab and imdevimab must be administered together (although packaged separately) after dilution by intravenous (IV) infusion only**
- Store casirivimab and imdevimab together in inventory. See **regencov.com/hcp/dosing/packaging** for images of packaging
- REGEN-COV 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
- **The authorized dosage is 1200 mg of casirivimab with 1200 mg of imdevimab administered together as a single intravenous (IV) infusion as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.** Since the optimal dosing regimen has not yet been established, it might be updated as data become available. See the **Fact Sheet for Healthcare Providers** for complete dosage, preparation, and administration instructions

- The prescribing healthcare provider and/or the provider's designee are responsible for mandatory reporting of all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. These adverse events must be reported within 7 calendar days from the onset of the event
- Healthcare facilities and providers must report therapeutics information and demonstrate adequate utilization via data reported through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services
- **MedWatch adverse event reports can be submitted to the FDA here, by using a postage-paid Form FDA 3500 and returning by mail/fax, or by calling 1-800-FDA-1088 to request a reporting form.** In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc via fax (1-888-876-2736) or email (medical.information@regeneron.com)

Refer to the **Fact Sheet for Healthcare Providers** and visit **regencov.com** for more information.
Please see **Important Safety Information** below.

IMPORTANT SAFETY INFORMATION

REGEN-COV™ (casirivimab with imdevimab) is an unapproved investigational therapy, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

- **Warnings and Precautions:**
  - **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (casirivimab with 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 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, arrythmia (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, dizziness, fatigue and diaphoresis. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care
  - **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, 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 REGEN-COV 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 REGEN-COV has not been observed in patients hospitalized due to 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 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
- **Adverse Reactions:**
  - Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the REGEN-COV 2,400-mg group, 2 (0.8%) patients in the REGEN-COV 8,000-mg group, and 6 (2.3%) patients in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg REGEN-COV), intestinal obstruction and dyspnea (8,000 mg REGEN-COV) and COVID-19, pneumonia and hypoxia (placebo). REGEN-COV **is not authorized at the 8,000-mg dose (4,000 mg casirivimab and 4,000 mg imdevimab)**
  - One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of Grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000-mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and included pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm, and none were reported in the 2,400-mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000-mg dose of REGEN-COV, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved
- **Patient Monitoring Recommendations:** Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete
- **Use in Specific Populations:**
  - **Pregnancy:** There is currently limited clinical experience in the use of REGEN-COV in COVID-19 patients who are pregnant. REGEN-COV therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus
  - **Lactation:** There is currently no clinical experience in the use of REGEN-COV in COVID-19 patients who are breastfeeding. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition

Refer to the **Fact Sheet for Healthcare Providers** and visit **regencov.com** for more information.