

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

**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, 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 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.

**RECENT MAJOR CHANGES**

- 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
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with co-formulation 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 6) 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

**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.
- 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.

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.

**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 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 (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age  $\geq 65$  years of age)
- Obesity or being overweight (for example, BMI  $> 25$  kg/m<sup>2</sup>, or if age 12-17, have BMI  $\geq 85$ th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](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.

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.

**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 Intravenous Infusion:**

- Co-formulated casirivimab and imdevimab solution in a vial and casirivimab and imdevimab solutions in individual vials which must be diluted prior to intravenous administration.
- Administer 600 mg of casirivimab and 600 mg of imdevimab together as a single intravenous infusion via pump or gravity (see [Table 1](#) and [Table 2](#)).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

#### **For Subcutaneous Injection:**

- Administer 600 mg of casirivimab and 600 mg of imdevimab using the co-formulated solution in a vial or using the individual vials (see [Table 3](#)).
- Clinically monitor patients after injections and observe patients for at least 1 hour after injections. Subcutaneous injection is an alternative route of administration when intravenous administration is not feasible and would lead to delay in treatment.

- The dosage of 600 mg of casirivimab and 600 mg of imdevimab for subcutaneous administration for treatment was 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)*].

REGEN-COV 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 REGEN-COV. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- 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 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 (18.1)*].
- 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](http://www.clinicaltrials.gov).

## **Contraindications**

None.

## **Dosing**

### Patient Selection and Treatment Initiation

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, 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 (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age  $\geq 65$  years of age)

- Obesity or being overweight (for example, BMI >25 kg/m<sup>2</sup>, 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](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

#### 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 600 mg of casirivimab and 600 mg of imdevimab together as a single intravenous infusion via pump or gravity (see [Table 1](#) and [Table 2](#)).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

#### For Subcutaneous Injection:

- Administer 600 mg of casirivimab and 600 mg of imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see [Table 3](#)).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

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

### 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)].

**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.**

- If either casirivimab or imdevimab in an 11.1 mL vial is available, you may prepare two doses of 600 mg of casirivimab and 600 mg of imdevimab simultaneously, 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.
- Unopened vials may be used to prepare an additional dose.

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

### **Preparation for Intravenous Infusion**

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](#)).
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 2](#)).
- 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 <sup>a</sup>
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:
100 mL		<ul style="list-style-type: none"> <li>• 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and</li> <li>• 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL)</li> </ul>
150 mL		
250 mL		and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below

<sup>a</sup> 600 mg of casirivimab and 600 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 1](#) and [Table 2](#)). Due to potential overflow 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 2: Recommended Administration Rate for Casirivimab and Imdevimab for Intravenous Infusion.**

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL <sup>a</sup>	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

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

### **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. 600 mg of casirivimab and 600 mg of imdevimab should be prepared using 4 syringes (Table 3). Obtain four 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and four 21-gauge 1½ inch transfer needles.
2. Withdraw 2.5 mL into each syringe (total of 4 syringes) (see Table 3). Prepare all 4 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 2°C to 8°C (36°F to 46°F) for no more than 4 hours or at room temperature up to 25°C (77°F) 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 3: 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



<b>Using Casirivimab and Imdevimab Co-formulated Vial</b>	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
<b>Using Casirivimab and Imdevimab Individual Vials</b>	<ul style="list-style-type: none"> <li>• <b>Casirivimab:</b> Withdraw 2.5 mL solution per syringe into TWO separate syringes.</li> <li>• <b>Imdevimab:</b> Withdraw 2.5 mL solution per syringe into TWO separate syringes.</li> </ul> <p style="text-align: center;">For total of 4 syringes.</p>

### **Administration for Subcutaneous Injection**

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see [Table 3](#)) 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

Benefit of treatment with REGEN-COV (casirivimab and imdevimab) 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 [*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 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 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 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](http://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 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 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.
3. Patients with known hypersensitivity to any ingredient of REGEN-COV must not receive REGEN-COV.
4. 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](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 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.
5. 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.
6. 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](mailto: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 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 <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 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.<sup>1</sup> As a health care provider, you must comply with the mandatory requirements of the 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 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 in 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 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](http://www.REGENCOV.com)  
If you have questions, please contact Regeneron at 1-844-734-6643.

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**END SHORT VERSION FACT SHEET**  
**Long Version Begins on Next Page**

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<sup>1</sup> 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.

## FULL EUA PRESCRIBING INFORMATION

### FULL EUA PRESCRIBING INFORMATION: CONTENTS\*

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

## 1 AUTHORIZED USE

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 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

- 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.
- 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 [*see Warnings and Precautions (5.2)*].

## 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 and Treatment Initiation

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 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 (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age  $\geq 65$  years of age)
- Obesity or being overweight (for example, BMI  $> 25$  kg/m<sup>2</sup>, or if age 12-17, have BMI  $\geq 85$ th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](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

### 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 600 mg of casirivimab and 600 mg of imdevimab together as a single intravenous infusion via pump or gravity (see [Table 1](#) and [Table 2](#)).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

### For Subcutaneous Injection:

- Administer 600 mg of casirivimab and 600 mg of imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see [Table 3](#)).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

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.

## 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)].

**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.**

- If either casirivimab or imdevimab in an 11.1 mL vial is available, you may prepare two doses of 600 mg of casirivimab and 600 mg of imdevimab simultaneously, 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.
- Unopened vials may be used to prepare an additional dose.

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

### **Preparation for Intravenous Infusion**

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](#)).
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 2](#)).

- 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 <sup>a</sup>
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:
100 mL		<ul style="list-style-type: none"> <li>• 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and</li> <li>• 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL)</li> </ul>
150 mL		
250 mL		and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below

<sup>a</sup> 600 mg of casirivimab and 600 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 1](#) and [Table 2](#)). 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 2: Recommended Administration Rate for Casirivimab and Imdevimab for Intravenous Infusion.**

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL <sup>a</sup>	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

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

### **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. 600 mg of casirivimab and 600 mg of imdevimab should be prepared using 4 syringes (Table 3). Obtain four 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and four 21-gauge 1½ inch transfer needles.
2. Withdraw 2.5 mL into each syringe (total of 4 syringes) (see Table 3). Prepare all 4 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 2°C to 8°C (36°F to 46°F) for no more than 4 hours or at room temperature up to 25°C (77°F) 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 3: 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	<ul style="list-style-type: none"> <li>• <b>Casirivimab:</b> Withdraw 2.5 mL solution per syringe into TWO separate syringes.</li> <li>• <b>Imdevimab:</b> Withdraw 2.5 mL solution per syringe into TWO separate syringes.</li> </ul> <p style="text-align: center;">For total of 4 syringes.</p>

**Administration for Subcutaneous Injection**

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see [Table 3](#)) 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

None.

## 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**

Benefit of treatment with REGEN-COV (casirivimab and imdevimab) 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 [*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**

Overall, more than 9,000 subjects have been exposed to intravenous REGEN-COV (casirivimab and imdevimab) in clinical trials in hospitalized and non-hospitalized subjects.

The safety of REGEN-COV (casirivimab and imdevimab) is based on analyses from, COV-2067, a Phase 1/2/3 trial of 6,311 ambulatory (non-hospitalized) subjects with COVID-19. 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.

The safety with subcutaneous administration is based on analysis from HV-2093, a randomized double-blind, placebo-controlled trial evaluating the safety and pharmacokinetic profile in healthy volunteer adult subjects. Subjects were randomized 3:1 to REGEN-COV (n=729) or placebo (n=240). Injection site reactions were observed in 12% and 4% of subjects following single dose administration in the casirivimab and imdevimab, and placebo arms respectively; the remaining safety findings with subcutaneous administration in the casirivimab and imdevimab arm were similar to the safety findings observed with intravenous administration in COV-2067.

## **7 PATIENT MONITORING RECOMMENDATIONS**

Clinically monitor patients during infusion 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](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 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](mailto: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 and HV-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 974 subjects randomized in Trial HV-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 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 (IgG1 $\kappa$ ) and imdevimab (IgG1 $\lambda$ ) 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 [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 (log<sub>10</sub> 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 4](#).

**Table 4: 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 <sup>1</sup>	Casirivimab	Imdevimab
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$C_{\text{eoi}}$ (mg/L) <sup>2</sup>	192 (80.9)	198 (84.8)
$C_{28}$ (mg/L) <sup>3</sup>	46.2 (22.3)	38.5 (19.7)

<sup>1</sup> Mean (SD)

<sup>2</sup> concentration at end of 1-hour infusion

<sup>3</sup> 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 5](#).

**Table 5: 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 <sup>1,5</sup>	Casirivimab	Imdevimab
$C_{\text{max}}$ (mg/L)	55.6 (22.2)	52.7 (22.5)
$t_{\text{max}}$ (day) <sup>2</sup>	8.00 (4.00, 87.0)	7.00 (4.00, 15.0)
$AUC_{0-28}$ (mg•day/L)	1060 (363)	950 (362)
$AUC_{\text{inf}}$ (mg•day/L) <sup>3</sup>	2580 (1349)	1990 (1141)
$C_{28}$ (mg/L) <sup>4</sup>	30.7 (11.9)	24.8 (9.58)
Half-life (day)	31.8 (8.35)	26.9 (6.80)

<sup>1</sup> Mean (SD)

<sup>2</sup> Median (range)

<sup>3</sup> Value reported for subjects with % $AUC_{\text{inf}}$  extrapolated <20%

<sup>4</sup> Observed concentration 28 days after dosing, i.e., on day 29

<sup>5</sup> 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

### 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<sub>50</sub> 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<sub>50</sub> values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudotyped VLP into FcγR2<sup>+</sup> Raji and FcγR1<sup>+</sup>/FcγR2<sup>+</sup> 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 (UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 6). 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.1.1351 lineage (South Africa origin), and all spike protein substitutions or key substitutions K417T+E484K, found in the P.1 lineage (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 (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 (California origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+K478T substitutions found in the B.1.617.2 lineage (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 (India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q, as indicated above.

**Table 6: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together**

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y <sup>a</sup>	no change <sup>d</sup>
B.1.351 (South Africa origin)	K417N, E484K, N501Y <sup>b</sup>	no change <sup>d</sup>
P.1 (Brazil origin)	K417T + E484K <sup>c</sup>	no change <sup>d</sup>
B.1.427/B.1.429 (California origin)	L452R	no change <sup>d</sup>
B.1.526 (New York origin) <sup>c</sup>	E484K	no change <sup>d</sup>

B.1.617.1/B.1.617.3 (India origin)	L452R+E484Q	no change <sup>d</sup>
B.1.617.2 (India origin)	L452R+K478T	no change <sup>d</sup>

<sup>a</sup> 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, T716L, S982A, D1118H.

<sup>b</sup> 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.

<sup>c</sup> 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

<sup>d</sup> No change:  $\leq 2$ -fold reduction in susceptibility.

<sup>e</sup> Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

It is not known how pseudotyped VLP data correlate with clinical outcomes.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction  $\geq 15\%$ , 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. 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<sub>10</sub> 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, but had no clear effects on viral load in lung tissue. The applicability of these findings to a clinical setting is not known.

## **18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA**

### **18.1 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<sub>10</sub> 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  $\geq 1$  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

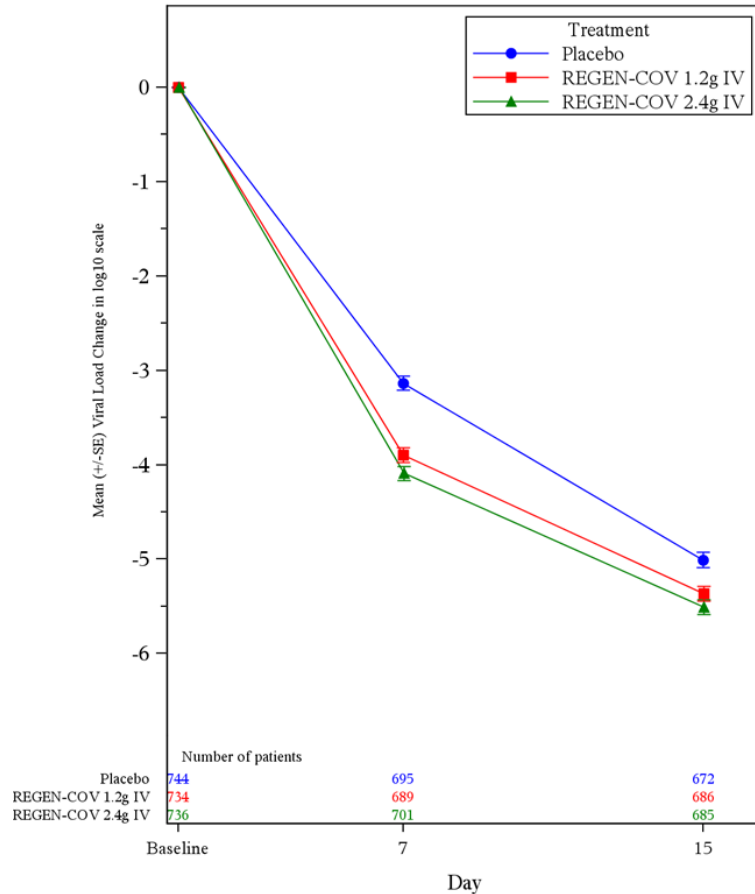
mg of casirivimab and 600 mg of imdevimab compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo (p=0.0024). Events occurred in 18 (1.3%) subjects treated with 1,200 mg of casirivimab and 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 7](#)). Results were consistent across subgroups of patients defined by nasopharyngeal viral load >10<sup>6</sup> copies/mL at baseline or serologic status.

**Table 7: Proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through day 29**

	<b>600 mg of casirivimab and 600 mg of imdevimab (intravenous)</b>	<b>Placebo</b>	<b>1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous)</b>	<b>Placebo</b>
	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<sub>10</sub> copies/mL) from baseline to Day 7 compared to placebo (-0.71 log<sub>10</sub> copies/mL for 600 mg dose of casirivimab and 600 mg of imdevimab and -0.86 log<sub>10</sub> 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<sup>6</sup> 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<sub>10</sub> copies/mL) to Day 15**



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).

## 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 8](#).

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 9](#).

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 9](#).

### **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 8: Co-Formulated Casirivimab and Imdevimab**

<b>Antibody</b>	<b>Concentration</b>	<b>Package Size</b>	<b>NDC Number</b>
<b>REGEN-COV (casirivimab and imdevimab)</b>	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 9: Individual Package Size**

<b>Antibody</b>	<b>Concentration</b>	<b>Package Size</b>	<b>NDC Number</b>
<b>Casirivimab REGN10933</b>	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
<b>Imdevimab REGN10987</b>	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 10](#).

**Table 10: Dose Pack Providing 1,200 mg Casirivimab and 1,200 mg Imdevimab**

<b>Dose Pack Size</b>	<b>Dose Pack Components</b>	<b>Concentration</b>	<b>Dose Pack NDC Number</b>
<b>2 Cartons</b>	<b>1 casirivimab REGN10933</b> (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-035-02
	<b>1 imdevimab REGN10987</b> (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	
<b>8 Cartons</b>	<b>4 casirivimab REGN10933</b> (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-036-08
	<b>4 imdevimab REGN10987</b> (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
<b>5 Cartons</b>	<b>1 casirivimab REGN10933</b> (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-037-05
	<b>4 imdevimab REGN10987</b> (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
<b>5 Cartons</b>	<b>4 casirivimab REGN10933</b> (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-038-05
	<b>1 imdevimab REGN10987</b> (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 2°C to 8°C (36°F to 46°F) for no more than 4 hours or at room temperature up to 25°C (77°F) 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](http://www.REGENCOV.com)  
If you have questions, please contact Regeneron at 1-844-734-6643.

### ***REGENERON***

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