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 the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. [see Limitations of Authorized Use]

• REGEN-COV has not been approved, but has been authorized for emergency use by FDA

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

• Healthcare providers should review the Fact Sheet for Healthcare Providers for information on the authorized use of REGEN-COV and mandatory requirements of the EUA and must comply with the requirements of the EUA. The FDA Letter of Authorization is available for reference, as well as the Dear Healthcare Provider Letter and Patient Fact Sheet

Limitations of Authorized Use

• REGEN-COV (casirivimab 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

Be sure to check regencov.com for periodic updates to the information contained in this guidebook.
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Executive summary

The COVID-19 pandemic is a global health crisis unlike any experienced in our lifetime. Regeneron has risen to this challenge with our 30 years of biotechnology expertise and deep experience in rapid response against global infectious diseases. Our science-driven culture and sense of responsibility to communities around the world galvanize us as we join in the fight against COVID-19.

About REGEN-COV

REGEN-COV consists of two monoclonal antibodies, casirivimab and imdevimab, which should be given together, and may be administered by intravenous (IV) 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.** REGEN-COV (casirivimab and imdevimab) is a dual monoclonal antibody (mAb) therapy designed specifically to block infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.

To develop REGEN-COV, Regeneron scientists evaluated thousands of fully human antibodies produced by the company's VelocImmune® mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19. The two virus-neutralizing mAbs that form REGEN-COV bind noncompetitively to the critical receptor-binding domain of the virus' spike protein. In preclinical studies, each variant of the virus showing reduced susceptibility to one mAb retained susceptibility to the other, and all clinical variants, including the Delta variant, retained susceptibility to the casirivimab and imdevimab combination. Circulating SARS-CoV-2 viral variants may be associated with resistance to mAbs. Health care providers should review the Antiviral Resistance information in Section 15 of the **Fact Sheet for Healthcare Providers** for details regarding specific variants and resistance, and refer to the **CDC website** as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

The development and manufacturing of REGEN-COV have been funded in part with federal funds from the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services under OT number: HHSO100201700020C.
About REGEN-COV (cont’d)

REGEN-COV is currently being studied in 2 ongoing Phase 2/3 clinical trials for the treatment of COVID-19 in certain hospitalized and outpatient patients, a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals and the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK. As of June 3rd, 2021, more than 9,000 subjects have been exposed to intravenous REGEN-COV in clinical trials in hospitalized and non-hospitalized subjects.

Use of REGEN-COV in patients hospitalized due to COVID-19 or in household contacts of infected individuals has not been granted authorization; these uses are not approved by any regulatory authority.

For more information on clinical trials testing the use of REGEN-COV, visit www.clinicaltrials.gov and see Appendix C of this guidebook.

This REGEN-COV EUA Guidebook compiles critical information, including Regeneron’s clinical trial experience with REGEN-COV, guidance from the National Infusion Center Association (NICA), and links to available resources, to assist health authorities and healthcare providers in planning and implementing treatment efforts against COVID-19. This guidebook should not supersede local requirements for sites of care or substitute for the medical judgment of treating healthcare professionals.

Healthcare providers should review the Fact Sheet for Healthcare Providers for information on the authorized use of REGEN-COV and mandatory requirements of the EUA. The FDA Letter of Authorization is available for reference, as well as the Dear Healthcare Provider Letter and Patient Fact Sheet.
SECTION 1:

Population for antibody treatment and important information for healthcare providers
Population for antibody treatment

**Authorized Use and Important Safety Information**

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 the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. [see Limitations of Authorized Use]

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

**Limitations of Authorized Use**

- REGEN-COV (casirivimab 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
Population for antibody treatment (cont’d)

The authorized dosage is

$$\begin{align*}
600\text{mg} \quad \text{casirivimab} & \quad + \quad 600\text{mg} \quad \text{imdevimab}
\end{align*}$$

administered together as a single intravenous (IV) 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. IV infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when IV infusion is not feasible and would lead to delay in treatment.

As of June 3rd, the previously authorized dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) is no longer authorized and should not be used.

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 ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m², 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
Population for antibody treatment
(cont’d)

- 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. Healthcare providers should review the Antiviral Resistance information in Section 15 of the Fact Sheet for Healthcare Providers for details regarding specific variants and resistance, and refer to the CDC website as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Available Dosage Forms of REGEN-COV:

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

1. A single vial which contains a combination of 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
Population for antibody treatment
(cont’d)

**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 Section 6 of this guidebook for additional information on dosing and administration
- 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 Section 6 of this guidebook for additional information on dosing and administration
- 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

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.
Healthcare 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.

- 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.
- 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 become 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).

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

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

**Warnings and Precautions:**

- **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under EUA. 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-syncpe, syncope), dizziness, fatigue and diaphoresis. Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

- **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 has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
• **Adverse Reactions:**
  - In a pooled phase 1/2/3 analysis of COV-2067, 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.
  - 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 casirivimab and 1,200 mg imdevimab, had 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.
  - 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.

• **Patient Monitoring Recommendations:** Clinically monitor patients during infusion and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete.

• **Use in Specific Populations:**
  - **Pregnancy:** There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.
  - **Lactation:** 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. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for REGEN-COV and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition.
SECTION 2:
Current supply and ongoing manufacturing effort
Current supply and ongoing manufacturing effort

Production of monoclonal antibodies is a complex, time- and labor-intensive process that requires deep expertise. Utilizing production and manufacturing platforms developed over decades, Regeneron rapidly scaled up REGEN-COV production, beginning in the early days of the pandemic with support from the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services.

All treatment sites can order REGEN-COV directly from AmerisourceBergen Corporation, the drug’s sole distributor. The product is free of charge to requesting sites.

Regeneron continues to increase in-house production of REGEN-COV, and the company has partnered with Roche to increase the global supply beginning in 2021. Regeneron will manufacture and distribute it in the United States, and Roche will develop, manufacture, and distribute it outside the United States. Once both companies are at full manufacturing capacity in 2021, at least 4 million treatment doses are expected to be available annually.

Be sure to visit regencov.com for periodic updates.
SECTION 3:
Ordering and administration sites
Access
All treatment sites must order REGEN-COV directly from AmerisourceBergen Corporation, the drug’s sole distributor. The product is free of charge to requesting sites.

Treatment sites should review the ASPR direct ordering process guide and place orders directly with AmerisourceBergen Corporation here.

Find Treatment Sites Near You
The United States and its territories partner with the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and the National Infusion Center Association (NICA) to provide a list of treatment site locations by state.

To find treatment centers where REGEN-COV and other antibody therapies for COVID-19 may be available, use the following treatment center locators:

Locate Infusion Centers (NICA)

Locate Infusion Centers (ASPR)

The U.S. government has set up a call center dedicated to providing patients and HCPs with information on monoclonal antibodies.

(English) 1-877-332-6585
(Spanish) 1-877-366-0310

*IMPORTANT INFORMATION: Treatment sites displayed in this tool have been authorized to administer antibody treatments for COVID-19-positive patients under Emergency Use Authorization. These antibody therapies are restricted to certain high-risk patients and require a drug order (similar to a prescription) from a healthcare provider (HCP) for eligible patients. HCPs must verify their patients’ eligibility and the availability of doses at an authorized treatment site before they refer their eligible patients to schedule an appointment to receive treatment. Please note that the inclusion of a site does not imply current availability of doses. More locations are regularly being added to both resources. Any questions related to distribution should be directed to AmerisourceBergen Corporation.*
Ordering and administration sites (cont’d)

FAQs

Is there a list of centers where REGEN-COV is available?

Details on treatment centers where antibody therapies can be administered, including REGEN-COV, can be found on the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and the National Infusion Center Association (NICA) site locators.

IMPORTANT INFORMATION: Treatment sites displayed in this tool have been authorized to administer antibody treatments for COVID-19-positive patients under Emergency Use Authorization. These antibody therapies are restricted to certain high-risk patients and require a drug order (similar to a prescription) from a healthcare provider (HCP) for eligible patients. HCPs must verify their patients’ eligibility and the availability of doses at an authorized treatment site before they refer their eligible patients to schedule an appointment to receive treatment. Please note that the inclusion of a site does not imply current availability of doses. More locations are regularly being added to both resources. Any questions related to distribution should be directed to AmerisourceBergen Corporation.

How can treatment sites order/re-order REGEN-COV?

To order REGEN-COV, treatment sites should visit the web order sheet to place a direct order request. Treatment sites should also review the ASPR direct ordering process guide found in Appendix B of this guidebook.

What is the coverage and reimbursement for REGEN-COV?

REGEN-COV is free of charge to requesting treatment sites, as the U.S. government is paying for the product. Claims may be submitted for the reimbursement of the drug administration only. Please see Section 4 of this guidebook for coding information.

Coverage and reimbursement of COVID-19–related treatments and procedures may vary from payer to payer; therefore, it is important that providers clarify and confirm coding/billing requirements with respective payers.
FAQs (cont’d)

Who determines which treatment sites receive REGEN-COV?

Treatment sites must order REGEN-COV directly from AmerisourceBergen Corporation, the drug’s sole distributor.

How is REGEN-COV supplied?

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

- **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
  OR

- **Individual antibody solutions in separate vials**, which may be in separate cartons or in a 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). Casirivimab and imdevimab vial labels and carton labeling may instead be labeled REGN10933 and REGN10987, respectively.

Product is shipped refrigerated (2 °C to 8 °C) to the administration site by AmerisourceBergen Corporation. As of June 2021, AmerisourceBergen Corporation is shipping co-formulated REGEN-COV, a single vial which contains a combination of two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab.

For important packaging information, see Section 5 of this guidebook.
Can dose pack material be exchanged for co-formulated product?

No. All drug is provided by the U.S. government. The government asks for sites to use dose pack material in stock prior to placing new orders for co-formulated product. Co-formulated product will enter distribution in June 2021. There is no plan to do an inventory exchange based on this direction from the U.S. government.

Can existing supply (i.e., product in circulation prior to June 2021) be used to supply the newly authorized lower dose (600 mg of casirivimab and 600 mg of imdevimab)?

Yes. Regardless of formulation (co-formulated solution containing two antibodies in a 1:1 ratio in a vial or individual antibody solutions in separate vials), one may prepare REGEN-COV at the new authorized dose. 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.

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.

**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.**

Can existing supply be used to administer either intravenous infusions or subcutaneous injections?

Yes. Although some REGEN-COV cartons and vial labels may have statements such as “Solution for Intravenous Administration” or “For Intravenous Infusion after Dilution” without language that states the subcutaneous route is appropriate, any of these vials may be used to prepare and administer intravenous infusions as well as subcutaneous injections. Please see Section 6 of this guidebook for instructions on the preparation and administration of REGEN-COV by intravenous infusion and subcutaneous injection.
Treatment sites can review the [ASPR direct ordering process guide](#) and place orders directly with AmerisourceBergen [here](#).
SECTION 4:

Coding and reimbursement
The following information is presented for informational purposes only and is not intended to guarantee or provide reimbursement or legal advice. Regeneron and its agents make no warranties or guarantees concerning the accuracy or appropriateness of this information for your particular use. The information in this guidebook is gathered from various resources and subject to change without notice. Payer coding requirements may vary or change over time, so it is important to regularly check with each payer to confirm payer-specific requirements.

The following information pertains to REGEN-COV therapy and administration:

- Review of relevant codes
  - International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Code
  - Level II Healthcare Common Procedure Coding System (HCPCS)
    - Administration code
    - Product code
  - National Drug Code (NDC)
  - Revenue Codes for Hospital Administration
- Additional considerations
Review of Relevant Codes

Codes should be confirmed with each respective payer, as there may be variability in both coding and documentation requirements.

INTERNATIONAL CLASSIFICATION OF DISEASES, TENTH REVISION, CLINICAL MODIFICATION (ICD-10-CM) DIAGNOSIS CODE

<table>
<thead>
<tr>
<th>Code^1,2</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>U07.1</td>
<td>COVID-19</td>
<td>For discharges on or after April 1, 2020, through the duration of the COVID-19 public health emergency period</td>
</tr>
</tbody>
</table>


Healthcare providers should refer to individual payer policies on COVID-19 billing and coding as appropriate.

LEVEL II HEALTHCARE COMMON PROCEDURE CODING SYSTEM (HCPCS) ADMINISTRATION CODE

<table>
<thead>
<tr>
<th>Code^3</th>
<th>Site of care</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0243</td>
<td>Outpatient (not including the home)</td>
<td>Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring</td>
</tr>
<tr>
<td>M0244</td>
<td>Home or residence</td>
<td>Intravenous infusion or subcutaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring in the home or residence; this includes a beneficiary’s home that has been made provider-based to the hospital during the COVID-19 public health emergency</td>
</tr>
</tbody>
</table>
LEVEL II HEALTHCARE COMMON PROCEDURE CODING SYSTEM (HCPCS) PRODUCT CODE

The following HCPCS code may be used to identify REGEN-COV.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q0244</td>
<td>Injection, casirivimab and imdevimab, 1,200 mg</td>
</tr>
</tbody>
</table>

Prior to June 3rd, 2021, the HCPCS code Q0243 (injection, casirivimab and imdevimab, 2,400 mg) was used to identify REGEN-COV. Providers may submit claims for patients given REGEN-COV prior to June 3rd using this code if appropriate/needed.

Select payers may require further claims documentation to better identify both casirivimab (REGN10933) and imdevimab (REGN10987), which could include but not be limited to:

- National Drug Codes (NDCs)
- Descriptor of monoclonal antibody name(s)
- Mode of administration

CASIRIVIMAB AND IMDEVIMAB NDC

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Concentration</th>
<th>Package size</th>
<th>NDCs for billing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-Formulated Casirivimab and</td>
<td>600 mg/600 mg per 10 mL (60 mg/60 mg per mL)</td>
<td>1 vial per carton</td>
<td>61755-0039-01</td>
</tr>
<tr>
<td>Imdevimab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casirivimab</td>
<td>1332 mg/11.1 mL (120 mg/mL)</td>
<td>1 vial per carton</td>
<td>61755-0024-01</td>
</tr>
<tr>
<td>Imdevimab</td>
<td>300 mg/2.5 mL (120 mg/mL)</td>
<td>1 vial per carton</td>
<td>61755-0026-01</td>
</tr>
<tr>
<td>Imdevimab</td>
<td>1332 mg/11.1 mL (120 mg/mL)</td>
<td>1 vial per carton</td>
<td>61755-0025-01</td>
</tr>
<tr>
<td>Imdevimab</td>
<td>300 mg/2.5 mL (120 mg/mL)</td>
<td>1 vial per carton</td>
<td>61755-0027-01</td>
</tr>
</tbody>
</table>

Note: casirivimab=REGN10933; imdevimab=REGN10987.

Product NDC numbers are 10 digits, however proper billing requires an 11-digit number in a 5-4-2 format. Converting NDCs from a 10-digit to an 11-digit format for billing requires an additional zero and is indicated in the table above in bold font.
DOSE PACK PROVIDING UP TO 2 TREATMENT DOSES (600 MG CASIRIVIMAB AND 600 MG IMDEVIMAB)\(^4\)

<table>
<thead>
<tr>
<th>Dose pack size</th>
<th>Dose pack components</th>
<th>Concentration</th>
<th>Dose pack NDCs for billing(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cartons</td>
<td>1 casirivimab REGN10933 (NDC 61755-024-01)</td>
<td>1,322 mg/11.1 mL (120 mg/mL)</td>
<td>61755-0035-02</td>
</tr>
<tr>
<td></td>
<td>1 imdevimab REGN10987 (NDC 61755-025-01)</td>
<td>1,322 mg/11.1 mL (120 mg/mL)</td>
<td></td>
</tr>
<tr>
<td>8 cartons</td>
<td>4 casirivimab REGN10933 (NDC 61755-026-01)</td>
<td>300 mg/2.5 mL (120 mg/mL)</td>
<td>61755-0036-08</td>
</tr>
<tr>
<td></td>
<td>4 imdevimab REGN10987 (NDC 61755-027-01)</td>
<td>300 mg/2.5 mL (120 mg/mL)</td>
<td></td>
</tr>
</tbody>
</table>

\(^4\)Product NDC numbers are 10 digits, however proper billing requires an 11-digit number in a 5-4-2 format. Converting NDCs from a 10-digit to an 11-digit format for billing requires an additional zero and is indicated in the table above in bold font.\(^5\)

REVENUE CODES FOR HOSPITAL ADMINISTRATION\(^6\)

Revenue codes allow hospitals to capture cost data for billing of services provided.

<table>
<thead>
<tr>
<th>Revenue code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Preventive care services, vaccine administration</td>
</tr>
<tr>
<td>0771</td>
<td>Pharmacy, drugs requiring detailed coding</td>
</tr>
</tbody>
</table>

\(^6\)Revenue codes allow hospitals to capture cost data for billing of services provided.
Additional Considerations

Since REGEN-COV will be made available by the government to providers at no cost during the initial EUA period, providers may not receive third-party payer reimbursement for the therapy when delivered in the hospital outpatient setting of care. However, providers may be able to obtain payment for the drug administration service. Providers should clarify claim submission requirements by payer, as the documentation may vary.

Since COVID-19 monoclonal antibody doses are provided by the government without charge, providers should only bill for the administration. Healthcare providers should not include the COVID-19 monoclonal antibody codes on the claim when the product is provided for free. However, CMS recognizes that many provider billing systems require a charge to be submitted, even when a product is provided for free or without charge. In this instance, physicians and non-physician practitioners bill the monoclonal antibody or COVID-19 immunization vaccine with a token charge of $0.01 (one penny). Providers should clarify all requirements by payer, as guidelines may vary by payer.

Healthcare professionals who provide these services to enrollees in a Medicare Advantage Plan should submit claims for monoclonal antibodies to treat COVID-19 that are covered by Part B in accordance with Section 3713 of the CARES Act to Traditional Medicare for all patients enrolled in Medicare Advantage in 2020 and 2021.

References:
SECTION 5:
Packaging guidance
**Packaging guidance**

**THERE ARE TWO DIFFERENT FORMULATIONS OF REGEN-COV:**

1. **CO-FORMULATED REGEN-COV**

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

   **Each vial of co-formulated REGEN-COV contains sufficient product to prepare one treatment dose.**

   Co-formulated REGEN-COV will not expire before March 31, 2023. The expiration date can be found on the co-formulation carton. If you have questions about the products’ expiration date, you may call Regeneron Medical Information at 1-844-734-6643.
Casirivimab and imdevimab are available as individual monoclonal antibody solutions in separate vials:

- Supplied in separate cartons, or
- Dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in configurations that include 2 and 8 cartons (see below)

Each REGEN-COV Dose Pack contains sufficient number of vials of casirivimab and imdevimab to prepare up to two treatment doses (600 mg of casirivimab and 600 mg of imdevimab).

Although some REGEN-COV cartons and vial labels may have statements such as “Solution for Intravenous Administration” or “For Intravenous Infusion after Dilution” without language that states the subcutaneous route is appropriate, any of these vials may be used to prepare and administer intravenous infusions as well as subcutaneous injections.

**REGEN-COV Dose Packs**

Each REGEN-COV Dose Pack contains 1,200 mg of casirivimab (REGN10933) and 1,200 mg of imdevimab (REGN10987). Casirivimab and imdevimab vial labels and carton labeling may instead be labeled REGN10933 and REGN10987, respectively.

The authorized dosage is 600 mg of casirivimab with 600 mg of imdevimab administered together as a single intravenous (IV) 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.

As of June 3rd, 2021, the previously authorized dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) is no longer authorized and should not be used.

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.

The cartons depicted in these dose packs may vary in appearance. See the following pages for variations in carton and vial labeling.
The dose packs’ expiry is based on the expiration dating of the vials included in the dose pack, and none will expire any earlier than May 31, 2022. If you are uncertain of when the products expire, you may call Regeneron Medical Information at 1-844-734-6643. Expiration dates for dose packs can be found on the packing slip within a shipment of material. Cartons in the dose pack may have different labeling, lot numbers, and expiration dates but none will expire any earlier than May 31, 2022.

Please note that all drug is provided by the U.S. government. The government asks for sites to use dose pack material in stock prior to placing new orders for co-formulated product. There is no plan to do an inventory exchange based on this direction from the U.S. government.
Single cartons of casirivimab and imdevimab may still be in distribution and you may encounter variations in carton and vial labeling. This is because some clinical trial supply is being made available to fulfill need during this public health emergency. Please see below for the two variations of carton and vial labeling for each antibody vial size.

**Casirivimab**

REGN10933

<table>
<thead>
<tr>
<th>2.5 mL</th>
<th>11.1 mL</th>
</tr>
</thead>
</table>

---

The diagram includes images of the carton and vial labels for both 2.5 mL and 11.1 mL vials of casirivimab.
Packaging guidance (cont’d)

Imdevimab
REGN10987

Some cartons do not include expiration. To obtain expiration dating, contact Regeneron Medical Information at medical.information@regeneron.com or call 1-844-734-6643
SECTION 6:
Preparation and administration instructions
Preparation and administration instructions

Storage and Handling

Casirivimab is preservative-free. Discard any unused portion.

Imdevimab is preservative-free. Discard any unused portion.

Co-formulated casirivimab and imdevimab is preservative-free. Discard unused portion.

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

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

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

If given by subcutaneous injections, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than 4 hours or at room temperature up to 25 ºC (77 ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.a

aThese times were based on preparation in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> Pharmaceutical Compounding–Sterile Preparations. If extenuating circumstances preclude immediate administration, manufacturer guidelines and National Infusion Center Association standards regarding stability, storage and preparation must be followed.
According to the National Infusion Center Association Standards, prepared product is intended for immediate administration to an individual patient. Administration of parenteral medications should begin immediately, ideally within 1 hour of beginning preparation. If extenuating circumstances preclude immediate administration, manufacturer guidelines and National Infusion Center Association standards regarding stability, storage and preparation must be followed.

**PREPARATION AND ADMINISTRATION INSTRUCTIONS (cont’d)**

REGEN-COV can be administered by IV infusion or by 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.

- 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.

As of June 2021,

The authorized dosage is

600 mg casirivimab + 600 mg imdevimab

administered together as a single intravenous (IV) 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.

As of June 3rd, 2021, the previously authorized dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) is no longer authorized and should not be used.

**REGEN-COV**

**Preparation and administration instructions (cont’d)**
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 vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vial(s).**

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

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

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

<table>
<thead>
<tr>
<th>Size of prefilled 0.9% Sodium Chloride infusion bag</th>
<th>Preparing using co-formulated casirivimab and imdevimab vial</th>
<th>Preparing casirivimab and imdevimab using individual vials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>Add 10 mL of co-formulated casirivimab and imdevimab (one vial) into a prefilled 0.9% Sodium Chloride infusion bag and administer as instructed on the following page</td>
<td>Individual vials may be supplied in dose packs</td>
</tr>
<tr>
<td>100 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 IV 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**

<table>
<thead>
<tr>
<th>Size of prefilled 0.9% Sodium Chloride infusion bag used</th>
<th>Maximum infusion rate</th>
<th>Minimum infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>180 mL/hr</td>
<td>20 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>21 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>250 mL</td>
<td>310 mL/hr</td>
<td>50 minutes</td>
</tr>
</tbody>
</table>

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

In June 2021, the maximum infusion rate when using the 50-mL infusion bag was adjusted down. The minimum infusion times were also lowered for the other bag sizes. These adjustments were made due to the change in authorized dose.
### Table 3: Gravity Drip Rate¹

**Drip Rates for 10-Drops/mL Administration Sets**

<table>
<thead>
<tr>
<th>VTBI (mL)</th>
<th>Duration (min)</th>
<th>Rate (mL/hr)</th>
<th>Drops per minute</th>
<th>Drops per 15 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>20</td>
<td>180</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>110</td>
<td>21</td>
<td>310</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>160</td>
<td>31</td>
<td>310</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>260</td>
<td>50</td>
<td>310</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

**Drip Rates for 15-Drops/mL Administration Sets**

<table>
<thead>
<tr>
<th>VTBI (mL)</th>
<th>Duration (min)</th>
<th>Rate (mL/hr)</th>
<th>Drops per minute</th>
<th>Drops per 15 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>20</td>
<td>180</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>110</td>
<td>21</td>
<td>310</td>
<td>78</td>
<td>19</td>
</tr>
<tr>
<td>160</td>
<td>31</td>
<td>310</td>
<td>78</td>
<td>19</td>
</tr>
<tr>
<td>260</td>
<td>50</td>
<td>310</td>
<td>78</td>
<td>19</td>
</tr>
</tbody>
</table>

**Drip Rates for 20-Drops/mL Administration Sets**

<table>
<thead>
<tr>
<th>VTBI (mL)</th>
<th>Duration (min)</th>
<th>Rate (mL/hr)</th>
<th>Drops per minute</th>
<th>Drops per 15 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>20</td>
<td>180</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>110</td>
<td>21</td>
<td>310</td>
<td>103</td>
<td>26</td>
</tr>
<tr>
<td>160</td>
<td>31</td>
<td>310</td>
<td>103</td>
<td>26</td>
</tr>
<tr>
<td>260</td>
<td>50</td>
<td>310</td>
<td>103</td>
<td>26</td>
</tr>
</tbody>
</table>

VTBI = volume to be infused over time.

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 vial(s).**

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

1. 600 mg of casirivimab and 600 mg of imdevimab should be prepared using four syringes (Table 4). Obtain four 3-mL or 5-mL polypropylene Luer lock syringes with Luer connection and four 21-gauge 1½-inch transfer needles.

2. Withdraw 2.5 mL into each syringe (total of four syringes) (see Table 4). Prepare all four syringes at the same time.
   - If individual vials of casirivimab and imdevimab are being used, consider labeling syringes during preparation to ensure the two syringes of casirivimab and two syringes of imdevimab are identifiable.

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.
## Preparation for Subcutaneous Injection

### TABLE 4: PREPARATION OF 600 MG OF CASIRIVIMAB AND 600 MG OF IMDEVIMAB FOR SUBCUTANEOUS INJECTIONS

<table>
<thead>
<tr>
<th>Prepare 600 mg of casirivimab and 600 mg of imdevimab</th>
<th>Preparation of four syringes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using casirivimab and imdevimab co-formulated vial</td>
<td>• Withdraw 2.5 mL solution per syringe into FOUR separate syringes</td>
</tr>
<tr>
<td>Using casirivimab and imdevimab individual vials</td>
<td>Casirivimab: Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use:</td>
</tr>
<tr>
<td></td>
<td>• Two vials of 2.5 mL</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>• One vial of 11.1 mL (approximately half of the vial)</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>Imdevimab: Withdraw 2.5 mL solution per syringe into TWO separate syringes. May use:</td>
</tr>
<tr>
<td></td>
<td>• Two vials of 2.5 mL</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>• One vial of 11.1 mL (approximately half of the vial)</td>
</tr>
<tr>
<td></td>
<td>For a total of four syringes</td>
</tr>
</tbody>
</table>
Administration for Subcutaneous Injection

• For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather four syringes (see Table 4) and prepared 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.
SECTION 7: Education and awareness
How SARS-CoV-2 infection starts

SARS-CoV-2 enters host cells by binding to the ACE2 receptor on the cell surface.²

SARS-CoV-2 interacts with ACE2 through the receptor-binding domain

- The spike protein is a trimeric protein composed of a “head” and “stem”²,³
- The “head” of the spike protein contains the recognition and attachment site for ACE2, known as the RBD.⁴
- The spike RBD has an “up” and “down” conformation, binding to ACE2 only in the “up” conformation.⁵

ACE2=angiotensin-converting enzyme 2; RBD=receptor-binding domain.
SARS-CoV-2 replicates within host cells to form new virus particles\textsuperscript{6,7}

1. The virus enters the host by first binding to ACE2 on the cell surface.
2. Once inside the cell, the virus releases its RNA.
3. Viral RNA is translated into proteins.
4. Some of these proteins form a replication complex to make more viral RNA.
5. Viral proteins and viral RNA are assembled into new virus particles.
6. New virus particles are released from the cell and proceed to infect other cells.

There are multiple routes of transmission\textsuperscript{8}


For more information about SARS-CoV-2, visit \texttt{regencov.com}.
Vaccines and antiviral monoclonal antibodies may help people with SARS-CoV-2
Antiviral monoclonal antibodies and vaccines are different, and both may help against COVID-19.9-11

**Pathogens** are harmful organisms that can invade the body, such as viruses or bacteria. Some molecules from these pathogens, called **antigens**, are recognized by B cells and prompt them to produce antibodies by the billions.9

**Antibodies** are typically Y-shaped proteins produced by the human body as part of a normal immune response to foreign molecules. Antibodies help fight off foreign substances to decrease or prevent their ability to cause sickness. Monoclonal antibodies can be made in the laboratory and given to someone whose immune system response may not be adequate or fast enough to fight an infection.10,11

When the human body encounters **pathogens** like SARS-CoV-2, the virus that causes COVID-19, the body’s immune system naturally produces **antibodies** to recognize and kill or neutralize the virus.9

The immune system typically remembers its reaction to a pathogen and can produce the same protective antibodies again in the future. This is called **immunological memory**.9
As the COVID-19 pandemic continues to threaten the health of people across the globe, everyone wants to know:

How can widespread immunity against this virus be achieved more quickly?

**Innate immunity** is the immunity you are born with. But the immunity you gain during your lifetime is called **adaptive immunity**, and it has 2 types: active and passive. **Active immunity** is conferred through endogenous antibodies, or antibodies found within the body whether through a previous infection or vaccination. **Passive immunity** is conferred through exogenous antibodies, or antibodies found outside of the body, such as in convalescent plasma or created in a laboratory. There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to reinfection.

The biopharmaceutical industry is researching ways to provide people with passive immunity through the use of antiviral monoclonal antibodies. Passive immunity can be achieved without infection and can be achieved faster than active immunity.
**Passive immunity**

Occurs immediately after receiving exogenous antibodies from an injection, infusion, or blood transfer.\(^1\)

**Antibody medicines**

Based on key principles of biology, these mimic the natural defenses and pathways of the immune system. Regeneron's core technologies allow for rapid and efficient generation of antiviral monoclonal antibodies outside of the body—corresponding to specific virus-neutralizing monoclonal antibodies.\(^9\)

Exogenous monoclonal antibodies are\(^8\):

- Derived from patients who have recovered from a particular virus
- OR
- Laboratory engineered

These monoclonal antibodies are then\(^14\):

- Put into a cell line that can produce the desired monoclonal antibody at scale.
- Grown at larger and larger quantities in bioreactors.
- Purified and packaged into vials.

For infectious diseases, Regeneron typically pursues a **combination antibody approach** of at least 2 monoclonal antibodies against a pathogen combined in a single medicine. The different monoclonal antibodies in a combination therapy work in slightly different ways to better neutralize the virus and to reduce the virus' ability to mutate.

This antiviral monoclonal antibody combination medicine is given:

As treatment: For sick patients administered via IV or by subcutaneous injection to block active infection

With this approach, immunity is provided immediately but is temporary.\(^11\)
Monoclonal antibodies block the virus’ ability to bind and infect the human cell.

Virus binds to receptor to infect healthy cells.

SARS-CoV-2

ACE2 receptor

With monoclonal antibodies

Monoclonal antibodies combination
Active immunity
Develops over time in response to an infection or vaccination.¹⁰

Vaccines
Used to induce the body's active immune response to protect from an infectious viral disease in the future, such as measles, the flu, or coronaviruses like SARS-CoV-2.¹⁵-¹⁷

A weakened, or attenuated, virus. A dead, or inactivated, form of the virus. A fragment of the virus.ᵃ Fragments of the virus' RNA or DNA.ᵃ

ᵃThese approaches are primarily being explored for vaccines to prevent COVID-19.¹⁵

To make many doses of vaccines, manufacturers¹⁸:
Gather needed key ingredients. Produce the antigen in large quantities. Package the antigen into an injection-ready form.

Vaccines work by:
Exposing healthy individuals to one of the items above via injection, which tricks the immune system into thinking the body is infected and generating a response.¹⁶,¹⁷

B cells in the vaccinated person's body begin producing protective antiviral antibodies in response.¹⁵ With time, active immunity is acquired.¹⁹

Developing active immunity takes time (days to weeks), but usually lasts longer (months to years). Experts don't yet know how long active immunity will last against COVID-19. Since it takes time to develop immunity from vaccines, they are not intended to treat patients with active infections.¹⁹,²⁰
Passive vs active immunity

Key takeaways

- Passive immunity and active immunity are both pathogen specific.
- The duration of active immunity is longer than that of passive immunity, but it takes longer to develop.
- Passive immunity is conferred through exogenous antibodies, or antibodies found outside of the body, such as in convalescent plasma or created in a laboratory.
- Active immunity is developed by the host antibodies in response to natural infection or administration of a vaccine.
- There are risks to both approaches, and healthcare providers and patients should weigh the benefits and risks to each individual and public health.

To learn more about passive vs active immunity, visit regencov.com.
References

SECTION 8:
Clinical data
Phase 3 study (COV-2067) of >4,500 patients at high risk for progression to severe COVID-19

STUDY DESIGN OF PHASE 3 TRIAL NCT04425629

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 1 of this guidebook.

PHASE 3 TRIAL RANDOMIZED 4,567 PATIENTS TO RECEIVE A SINGLE IV INFUSION

The two REGEN-COV doses at the start of Phase 3 were 8,000 mg and 2,400 mg; however, based on Phase 1/2 efficacy analyses showing that the 8,000-mg and 2,400-mg doses were similar, the Phase 3 portion of the protocol was amended to compare 2,400-mg dose vs placebo and 1,200-mg dose vs placebo.

Comparisons were between patients randomized to specific REGEN-COV doses and patients concurrently randomized to placebo.
Phase 3 study (COV-2067) of >4,500 patients at high risk for progression to severe COVID-19 (cont’d)

Endpoints included:

• Primary endpoint: proportion of subjects with ≥1 COVID-19–related hospitalization or all-cause death through Day 29

• Secondary endpoints included:
  ○ Median time to COVID-19 symptom resolution as recorded in a trial-specific daily symptom diary
  ○ Change from baseline in SARS-CoV-2 viral load (log10 copies/mL) at Day 7

**BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>50 years</td>
</tr>
<tr>
<td>≥65 years of age</td>
<td>13% of patients</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52% of patients</td>
</tr>
<tr>
<td>Male</td>
<td>48% of patients</td>
</tr>
<tr>
<td><strong>Race and ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>84% of patients</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>36% of patients</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5% of patients</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>≥1 risk factors for severe COVID-19</td>
<td>100% of patients</td>
</tr>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Median duration of symptoms</td>
<td>3 days</td>
</tr>
<tr>
<td><strong>Viral load</strong></td>
<td></td>
</tr>
<tr>
<td>Mean viral load at baseline</td>
<td>6.2 log10 copies/mL</td>
</tr>
</tbody>
</table>

• The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups
A statistically significant, 70% reduction in COVID-19–related hospitalization or all-cause death

In a Phase 3 trial (COV-2067) conducted over 29 days in over 4,000 subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization and with at least one factor for severe coronavirus disease 2019 (COVID-19), i.e., the modified full analysis set (mFAS):

| PRIMARY ENDPOINT: PROPORTION OF PATIENTS WITH ≥1 COVID-19–RELATED HOSPITALIZATION OR ALL-CAUSE DEATH THROUGH DAY 29 |
|--------------------------------------------------|--------------------------------------------------|----------------------------------------------------------|
| REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab) intravenous (n=736) | Placebo (n=748) | 1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous) (n=1,355) | Placebo (n=1,341) |
| # of patients with events | 7 (1.0%) | 24 (3.2%) | 18 (1.3%) | 62 (4.6%) |
| Risk reduction | 70% compared to placebo ($P=0.0024$) | 71% compared to placebo ($P<0.0001$) |

- 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 is no longer authorized under the EUA, as of June 3rd, 2021. Results were consistent across subgroups of patients including nasopharyngeal viral load $>10^6$ copies/mL or serologic status at baseline
- In the 1,200-mg analysis, there was one death each in the REGEN-COV and placebo arm ($P=1.0$); and in 2,400-mg analysis, there were one and three deaths, respectively, in the REGEN-COV and placebo arms ($P=0.3721$).
A statistically significant, 29% reduction in time to symptom resolution

In a Phase 3 trial (COV-2067) conducted over 29 days in over 4,000 subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization and with at least one factor for severe coronavirus disease 2019 (COVID-19), i.e., the modified full analysis set (mFAS):

**KEY SECONDARY ENDPOINT: MEDIAN TIME TO COVID-19 SYMPTOM RESOLUTION (IN DAYS)**

<table>
<thead>
<tr>
<th></th>
<th>REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab) intravenous (n=736)</th>
<th>Placebo (n=748)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days to symptom resolution</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>
| Median reduction (days) | 4  
(P=0.0001)                                                                    |                 |

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).
Statistically significant reduction in viral load

Reductions in LS mean viral load with REGEN-COV through Day 15 vs placebo

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

CHANGE FROM BASELINE IN SARS-CoV-2 VIRAL LOAD (log_{10} COPIES/mL) TO DAY 15

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>REGEN-COV 1.2 g IV (600 mg of casirivimab and 600 mg of imdevimab)</th>
<th>REGEN-COV 2.4 g IV (1,200 mg of casirivimab and 1,200 mg of imdevimab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>744</td>
<td>695</td>
<td>672</td>
</tr>
<tr>
<td></td>
<td>734</td>
<td>689</td>
<td>686</td>
</tr>
<tr>
<td></td>
<td>736</td>
<td>701</td>
<td>685</td>
</tr>
</tbody>
</table>

Mean (+/-SE) viral load change in log_{10} scale

IV=intravenous; LS mean=least squares mean; SE=standard error.
Safety profile in the clinical trials

**INTRANOVOUS INFUSION SAFETY DATA**

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 casirivimab and 4,000-mg imdevimab dose. The 1,200-mg casirivimab and 1,200-mg imdevimab dose is no longer authorized under this EUA, as of June 3rd, 2021.

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.

<table>
<thead>
<tr>
<th>Infusion-related reactions resulting in permanent discontinuation of the infusion (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash)</th>
<th>600 mg of casirivimab and 600 mg of imdevimab (n=827)</th>
<th>1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,849)</th>
<th>4,000 mg of casirivimab and 4,000 mg of imdevimab (n=1,012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*a All infusion-related events resolved.

*b REGEN-COV is not authorized at the 1,200-mg casirivimab and 1,200-mg imdevimab dose.

*c REGEN-COV is not authorized at the 4,000-mg casirivimab and 4,000-mg imdevimab dose.

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.
SUBCUTANEOUS INJECTION SAFETY DATA

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).

<table>
<thead>
<tr>
<th></th>
<th>600 mg of casirivimab and 600 mg of imdevimab (n=729)</th>
<th>Placebo (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of subjects with</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>injection site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactions following</td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration of a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (see previous page).
Clinical data

Important Safety Information

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

- **Warnings and Precautions:**
  - **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under EUA. 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. Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs
  - **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 has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19–related comorbidity
Important Safety Information (cont’d)

• **Adverse Reactions:**
  ◦ In a pooled phase 1/2/3 analysis of COV-2067, 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.
  ◦ 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 casirivimab and 1,200 mg imdevimab, had 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.
  ◦ 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.

• **Patient Monitoring Recommendations:** Clinically monitor patients during infusion and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete.

• **Use in Specific Populations:**
  ◦ **Pregnancy:** There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.
  ◦ **Lactation:** 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. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for REGEN-COV and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition.

For more clinical data, visit regencov.com to view the antiviral and clinical profile of REGEN-COV.
IMPORTANT PRESCRIBING INFORMATION

Subject: Important information on new co-formulated REGEN-COV™ (casirivimab and imdevimab) product, a lower authorized dose, an additional alternative route of administration (subcutaneous), and the updated treatment indication including expanded high-risk criteria for Regeneron COVID-19 Monoclonal Antibodies.

Dear Healthcare Provider:

The purpose of this notice is to make you aware of new information regarding REGEN-COV™ (casirivimab and imdevimab). The following chart highlights the pertinent new information, but is not inclusive of all changes to the Healthcare Providers (HCP) Fact Sheet.

CHART 1. SUMMARY OF RECENT MAJOR CHANGES

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
<th>Further info located</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage and Administration (Box, Section 2.2)</td>
<td>Updated authorized dosage to 600 mg of casirivimab and 600 mg of imdevimab.</td>
<td>Page 2</td>
</tr>
<tr>
<td>Dosage and Administration (Box, Section 2.2 and 2.4)</td>
<td>Addition of subcutaneous route of administration as an alternative route when intravenous infusion is not feasible and would lead to delay in treatment.</td>
<td>Page 2</td>
</tr>
<tr>
<td>Dosage and Administration (Box, Section 2.2 and 2.4)</td>
<td>Addition of new REGEN-COV co-formulated product in single vial.</td>
<td>Page 2</td>
</tr>
<tr>
<td>Authorized Use</td>
<td>Expanded the definition of progression of severe COVID-19 to include death.</td>
<td>Page 2</td>
</tr>
<tr>
<td>Dosage and Administration (Box, Section 2.1)</td>
<td>Expanded high-risk criteria for patient selection.</td>
<td>Page 3</td>
</tr>
</tbody>
</table>

REGEN-COV™ (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab to be administered together) are authorized for use under an Emergency Use Authorization (EUA) for treatment of SARS-CoV-2 infection.
New Authorized Lower Dose of REGEN-COV

The Phase 3 clinical efficacy and safety endpoints from study COV-2067 in ambulatory patients with COVID-19 demonstrated consistent results across doses of 600 mg of casirivimab and 600 mg of imdevimab and 1,200 mg of casirivimab and 1,200 mg of imdevimab. Based on these data, the dose authorized for REGEN-COV (casirivimab and imdevimab) has been lowered.

The new recommended dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab, administered together.

New Subcutaneous Route of Administration

REGEN-COV (casirivimab and imdevimab) 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. 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.

New REGEN-COV Co-formulated Product in Single Vial

REGEN-COV (casirivimab and imdevimab) co-formulated product, NDC 61755-039-01, containing two antibodies in a 1:1 ratio of casirivimab and imdevimab in a single vial is now authorized. Each 10 mL vial includes 600 mg of casirivimab and 600 mg of imdevimab. The REGEN-COV co-formulated product may be used to prepare a single treatment dose to be administered by intravenous infusion or subcutaneous injection. Images of the product packaging for REGEN-COV co-formulated product are provided as Attachment 1 at the end of the document.

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 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.

LIMITATIONS FOR 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.

Expanded High-risk Criteria for Patient Selection

Treatment is now authorized in anyone with onset within the past 10 days of symptomatic COVID-19 who is deemed by the HCP as being at increased risk of severe COVID-19, including having an increased risk of hospitalization or death due to COVID-19. To assist in this determination, patient selection criteria were expanded to reference the known information identified by the Centers for Disease Control on factors that put individuals at higher risk for progressing to severe COVID-19. The selection criteria are provided as Attachment 2 at the end of the letter and in the HCP fact sheet Section 2.1.

HCP Action when Using REGEN-COV

In light of these updates and additions to the authorized dosage and route of administration, healthcare providers should update their Electronic Health Records (EHRs) with the new product information including the new authorized dosage to guide the prescribing of REGEN-COV and to allow for the use of current supplies to appropriately treat patients.

Preparation and administration instructions in the HCP Fact Sheet have been updated to reflect the new authorized dosage and route of administration. Stay current with the latest Fact Sheet for Health Care Providers by visiting (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf)

All existing REGEN-COV vials may be used to prepare doses for intravenous infusion as well as subcutaneous injection. Although some REGEN-COV cartons and vial labels may have statements such as “Solution for Intravenous Administration” or “For Intravenous Infusion after Dilution” without language that states the subcutaneous route is appropriate, any of these vials may be used to prepare and administer intravenous infusions as well as subcutaneous injections.

Preparation of the 600 mg of casirivimab and 600 mg of imdevimab dose can be prepared with the REGEN-COV dose packs currently in distribution or the co-formulated product once that product becomes available. If you have REGEN-COV dose packs, it is important to note that the material in each dose pack is sufficient to make two 600 mg of casirivimab and 600 mg of imdevimab doses.1

1 As a reminder, casirivimab and imdevimab are packaged and have been made available to the marketplace in various sizes and configurations. Pharmacists are urged to carefully review the labeling for each carton or package and properly combine the appropriate quantity of vials to obtain the authorized dose (See Section 19 HOW
• If desired, two doses may be prepared simultaneously according to the direction provided in the HCP Fact Sheet.

• Keep any unused, unopened vials of casirivimab and imdevimab together in the refrigerator to avoid medication errors.

• All REGEN-COV vials are preservative-free. **Once punctured, the vials should be discarded after 4 hours.**

Resources to help clarify dose preparation can be found on [www.REGENCOV.com](http://www.REGENCOV.com).

*Considerations specific to administration of REGEN-COV by intravenous infusion*

• For intravenous infusion, consider enabling EHR alerts to remind providers that casirivimab and imdevimab must be diluted prior to intravenous infusion and infused together using a single intravenous bag.

• Have the intravenous dose preparation information for casirivimab and imdevimab available to those preparing the medication.

• If preparing two intravenous bags simultaneously from a dose pack, it is recommended to have an independent double check of the drawn up medications in the syringes prior to injecting into the intravenous bags to prevent medication errors.

• The intravenous bag may be stored under refrigeration 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.

*Considerations specific to administration of REGEN-COV by subcutaneous injection*

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

• Have the subcutaneous dose preparation information for casirivimab and imdevimab available to those preparing the medication.

• If preparing two subcutaneous treatment doses simultaneously from a dose pack for a total eight prefilled syringes, it is recommended to have an independent double check of the drawn up medications in the syringes and clearly labeled syringe contents at the time of preparation.

• The prepared syringes for subcutaneous administration may be stored under refrigeration at 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 hours.

*Patient Counseling Information*

• Instruct patients to review the Fact Sheet for Patients, Parents, & Caregivers.
Patients who are 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.

If medically appropriate for the patient to receive a COVID-19 vaccine, providers should counsel patients that REGEN-COV does not replace vaccination against COVID-19.

- Counsel patients to record the date of REGEN-COV administration.
- Providers may consider recommending that patients schedule COVID-19 vaccination as soon as they are eligible according to local/state public health guidelines but no earlier than 90 days after REGEN-COV administration.

**Reporting Adverse Events and Medication Errors**

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

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

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

Please provide a copy of all FDA MedWatch forms to Regeneron via fax (1-888-876-2736) or email (medical.information@regeneron.com).

The EUA Fact Sheet for Healthcare Providers is included with this notice, available at [www.REGENCOV.com](http://www.REGENCOV.com), or available by scanning the QR Code below:

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2 There are currently no data on the safety and effectiveness of the Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccines in people who received REGEN-COV. Based upon the low risk of reinfection and the estimated half-life of the monoclonal antibodies to treat COVID-19, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) recommends COVID-19 vaccination be deferred for at least 90 days after treatment with a monoclonal antibody for COVID-19. Updates to the ACIP recommendation may be made as additional information on the interaction between prior monoclonal antibody treatment and vaccine response becomes available.
Johnathan Lancaster, MD, PhD
Senior Vice President, Global Medical Affairs

Enclosure: EUA Fact Sheet for Healthcare Providers
1. Images of the REGEN-COV Coformulation Presentation Packaging
2. High-risk patient criteria
The following medical conditions or other factors that may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk of progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m², or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above.

For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.
APPENDIX B:

Overview of direct order system
Overview of Direct Order Process for COVID-19 Therapeutics

Purpose:
The United States Government (USG) is responsible for the allocation and distribution of monoclonal antibody (mAb) therapeutics for the treatment of COVID-19 as per the Emergency Use Authorizations (EUA) issued by the U.S. Food and Drug Administration (FDA). The USG has developed a process for sites to directly order from the distributor, AmerisourceBergen (ABC).

Process overview:
- Sites (based on classes of trade), are able to order bamlanivimab (Lilly) and/or casirivimab/imdevimab (Regeneron) monoclonal antibodies for their facilities at the link listed below
- Sites will be required to:
  - Provide ABC with a board of pharmacy license or physician letter of authorization
  - Attest to their designated class of trade and that they will administer the authorized product according to the terms of the FDA issued EUA
  - Provide utilization data via either TeleTracking or NHSN
- Sites can order product based on established minimum amounts; subsequent orders are subject to a maximum amount based on previous orders and utilization
- State departments of health will be informed of therapies ordered within their jurisdictions for awareness.

Link to order: https://app.smartsheet.com/b/form/255d164d67834793b4ab549e160941e8

Required utilization reporting:
- Weekly reporting on these therapeutics is required every Wednesday through HHS Protect, TeleTracking, or CDC's National Healthcare Safety Network (NHSN) depending on facility type
- Instructions are included at the bottom of the ABC order form, and included here for reference
  - To improve availability of treatments for Monoclonal Antibody (mAb) therapies for COVID patients across the nation, the federal government requires entities receiving shipments of mAb treatments to provide weekly reports of mAb treatments administered and stocks on hand through one of the following reporting mechanisms:
    - Skilled Nursing Facilities / Long Term Care Facilities are requested to provide data through the CDC's NHSN data system at a future date (Guidance forthcoming)
    - All Additional Facilities such as Dialysis Centers, Home Health Services, Oncology, and Infusion Centers, are required to provide the requested data through the following portal: https://teletracking.protect.hhs.gov/
  - First-time users will receive enrollment and reporting instructions in an e-mail from protect-noreply@hhs.gov with the subject line of “Invitation: HHS TeleTracking COVID-19 Portal.” This email provides step-by-step instructions to access the Portal for the first time. If you do not receive an email in the next 48 hours, please contact TeleTracking's Technical Support at hhs-protect@teletracking.com
APPENDIX C:

Ongoing clinical trials
REGEN-COV is currently being studied in 2 ongoing Phase 2/3 clinical trials for the treatment of COVID-19 in certain hospitalized patients and outpatient patients, a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals, and the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK. As of June 3rd, 2021, more than 9,000 subjects have been exposed to intravenous REGEN-COV in clinical trials in hospitalized and non-hospitalized subjects.

Use of REGEN-COV in patients hospitalized due to COVID-19 or in household contacts of infected individuals has not been granted authorization; these uses are not approved by any regulatory authority.

For more information on clinical trials testing the use of REGEN-COV, see the following table:

<table>
<thead>
<tr>
<th>Trial focus</th>
<th>Phase</th>
<th>Patient population</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Phase 2/3</td>
<td>Outpatient ambulatory adult and pediatric patients×</td>
<td>NCT04425629</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 2/3</td>
<td>Certain hospitalized adult patients</td>
<td>NCT04426695, Active, not currently recruiting</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 3</td>
<td>Hospitalized patients (RECOVERY trial)</td>
<td>NCT04381936, Not currently recruiting U.S. patients</td>
</tr>
<tr>
<td>Prevention</td>
<td>Phase 3</td>
<td>Healthy adults and children who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay</td>
<td>NCT04452318, Active, not currently recruiting</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 2</td>
<td>Outpatient ambulatory adult patients</td>
<td>NCT04666441, Active, not currently recruiting</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 1</td>
<td>Healthy adults</td>
<td>NCT04519437, Active, not currently recruiting</td>
</tr>
<tr>
<td>Use with mRNA vaccine</td>
<td>Phase 2</td>
<td>Healthy adults or adults with chronic stable illness</td>
<td>NCT04852978, Not yet recruiting</td>
</tr>
</tbody>
</table>

×Due to recommendation from independent data monitoring committee (IDMC), enrollment of placebo patients has been halted due to reducing the rate of hospitalization and death with REGEN-COV compared to placebo.
APPENDIX D: FAQs
FAQs

Access and reimbursement

What is an Emergency Use Authorization (EUA)?

An EUA allows the U.S. Food and Drug Administration (FDA) to help strengthen the nation’s public health protections against chemical, biological, radiological, and nuclear (CBRN) defense threats by facilitating the availability and use of therapies needed during public health emergencies.

Under section 564 of the Federal Food, Drug, and Cosmetic Act, the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.

Is there a list of centers where REGEN-COV is available?

Details on treatment centers where antibody therapies can be administered, including REGEN-COV, can be found on the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and the National Infusion Center Association (NICA) site locators.

*IMPORTANT INFORMATION: Treatment sites displayed in this tool have been authorized to administer antibody treatments for COVID-19-positive patients under Emergency Use Authorization. These antibody therapies are restricted to certain high-risk patients and require a drug order (similar to a prescription) from a healthcare provider (HCP) for eligible patients. HCPs must verify their patients’ eligibility and the availability of doses at an authorized treatment site before they refer their eligible patients to schedule an appointment to receive treatment. Please note that the inclusion of a site does not imply current availability of doses. More locations are regularly being added to both resources. Any questions related to distribution should be directed to AmerisourceBergen Corporation.

How can treatment sites order/re-order REGEN-COV?

To order REGEN-COV, treatment sites should visit the web order sheet to place a direct order request. Treatment sites should also review the ASPR direct ordering process guide found in Appendix B of this guidebook.
What is the coverage and reimbursement for REGEN-COV?

REGEN-COV is free of charge to requesting treatment sites, as the United States government is paying for the product. Claims may be submitted for the reimbursement of the drug administration only. Please see Section 4 of this guidebook for coding information.

Coverage and reimbursement of COVID-19–related treatments and procedures may vary from payer to payer; therefore, it is important that providers clarify and confirm coding/billing requirements with respective payers.

Who determines which treatment sites receive REGEN-COV?

Treatment sites must order REGEN-COV directly from AmerisourceBergen Corporation, the drug’s sole distributor.

Packaging and preparation

Why are there different formulations and types of packages for REGEN-COV?

There are TWO different formulations of REGEN-COV:

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

**Each vial of co-formulated REGEN-COV contains sufficient product to prepare one treatment dose.**

Casirivimab and imdevimab available as individual monoclonal antibody solutions in separate vials:

- supplied in separate cartons, or
- dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations may vary in vial size, strength, and appearance and are available in dose pack configurations that include 2 and 8 cartons

**Each REGEN-COV Dose Pack contains sufficient number of vials of casirivimab and imdevimab to prepare up to two treatment doses (600 mg of casirivimab and 600 mg of imdevimab).**

Although some REGEN-COV cartons and vial labels may have statements such as “Solution for Intravenous Administration” or “For Intravenous Infusion after Dilution” without language that states the subcutaneous route is appropriate, any of these vials may be used to prepare and administer intravenous infusions as well as subcutaneous injections.
When does REGEN-COV expire?

The dose packs’ expiry is based on the expiration dating of the vials included in the dose pack, and none will expire any earlier than May 31, 2022.

Co-formulated REGEN-COV will not expire before March 31, 2023. The expiration date can be found on the co-formulation carton. If you have questions about the products’ expiration date, you may call Regeneron Medical Information at 1-844-734-6643.

Does casirivimab or imdevimab packaging include latex?

For both formulations of REGEN-COV (co-formulated solution or individual antibody solutions in separate vials), the vial stoppers are not made with natural rubber latex.

Does the prepared IV bag need to be protected from light?

Prepared IV bags of casirivimab and imdevimab do not require protection from ambient light.

What are my options if I can’t administer the drug immediately?

**Intravenous administration:** 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.

**Subcutaneous administration:** If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than 4 hours or at room temperature up to 25 ºC (77 ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Clinical data

How does REGEN-COV work?

The combination of casirivimab and imdevimab makes up REGEN-COV, Regeneron’s investigational anti-viral antibody combination being studied in COVID-19. It consists of two noncompeting, virus-neutralizing monoclonal antibodies.

Casirivimab and imdevimab bind simultaneously to different, non-overlapping epitopes on severe acute respiratory syndrome 2 (SARS-CoV-2) spike (S) glycoprotein.
Can patients who have already been vaccinated for COVID-19 still receive REGEN-COV?

Yes. Patients who have received a COVID-19 vaccine can still receive monoclonal antibody therapy if they meet the authorized use criteria for REGEN-COV. Healthcare providers should consider the benefit-risk for an individual patient. HCPs may also call Regeneron Medical Information at 1-844-734-6643 for additional information.

Does REGEN-COV protect against viral variants that have emerged?

REGEN-COV has been tested against, and was found to retain neutralization activity against, pseudotyped virus-like particles (VLP) expressing the spike protein substitution(s) defined in the below SARS-CoV-2 clinical variants. It is not known how pseudotyped VLP data correlate with clinical outcomes.

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.

- **B.1.1.7** (United Kingdom origin [Alpha]). REGEN-COV retained neutralization activity against all spike protein substitutions.
- **B.1.351** (South Africa origin [Beta]). REGEN-COV retained neutralization activity against all spike protein substitutions.
- **B.1.427/B.1.429** (California origin [Epsilon]). REGEN-COV retained neutralization activity against the L452R spike protein substitution.
- **P.1** (Brazil origin [Gamma]). REGEN-COV retained neutralization activity against the K417T + E484K spike protein substitution.
- **B.1.526** (New York origin [Iota]). REGEN-COV retained neutralization activity against the E484K spike protein substitution.
- **B.1.617.1/B.1.617.3** (India origin [Kappa]). REGEN-COV retained neutralization activity against the L452R + E484Q spike protein substitution.
- **B.1.617.2** (India origin [Delta]). REGEN-COV retained neutralization activity against the L452R + K478T spike protein substitution.

Healthcare providers should review the Antiviral Resistance information in Section 15 of the Fact Sheet for Healthcare Providers for details regarding specific variants and resistance, and refer to the CDC website as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

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The Greek names of each SARS-CoV-2 variant have been designated by the WHO.

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*a* As of June 3, 2021.

*b* Defined as ≤2-fold reduction in susceptibility.

*c* 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, del1145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

*d* 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.

*e* Casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K (which are found in this variant).

*f* Casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K.

*g* Casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484K.

*h* Not all isolates of the New York lineage harbor E484K substitution (as of February 2021).

*i* Casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q.
Is REGEN-COV recommended by third-party treatment guidelines?

On April 8, 2021, REGEN-COV (casirivimab and imdevimab) received an AIIa recommendation in the National Institutes of Health (NIH) COVID-19 Treatment Guidelines for treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression:

- Rating of Recommendation: A (strong)
- Rating of Evidence: IIa (other randomized trials or subgroup analyses of randomized trials)

The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in their guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website.

What are my requirements for reporting medication errors and serious adverse events?

Prescribing healthcare professionals and/or the provider’s designee are responsible for mandatory reporting of all medication errors and ALL SERIOUS ADVERSE EVENTS potentially related to REGEN-COV. These adverse events must be reported within 7 calendar days from the onset of the event. MedWatch adverse event reports can be submitted to the FDA online here by submitting a postage-paid Form FDA 3500 and returning by mail/fax, or by calling 1-800-FDA-1088 to request a reporting form. In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc via fax (1-888-876-2736) or email (medical.information@regeneron.com). See the Fact Sheet for Healthcare Providers for detailed information about the obligation to report medication errors and serious adverse events.

Are there any warnings associated with use of this monoclonal antibody combination therapy?

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

- **Warnings and Precautions:**
  - **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under EUA. 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.
FAQs (cont'd)

Are there any warnings associated with use of this combination therapy? (cont’d)

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

- **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 has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19–related comorbidity.
What adverse reactions have been identified thus far in the randomized trials?

- In a pooled phase 1/2/3 analysis of COV-2067, 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.
- 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 casirivimab and 1,200 mg imdevimab, had 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.
- 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.
Who is eligible for REGEN-COV under the EUA?

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 the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. [see Limitations of Authorized Use]

REGEN-COV has not been approved, but has been authorized for emergency use by FDA

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

- Healthcare providers should review the Fact Sheet for Healthcare Providers for information on the authorized use of REGEN-COV and mandatory requirements of the EUA and must comply with the requirements of the EUA. The FDA Letter of Authorization is available for reference, as well as the Dear Healthcare Provider Letter and Patient Fact Sheet

Limitations of Authorized Use

- REGEN-COV (casirivimab 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
Who is eligible for REGEN-COV under the EUA? (cont’d)

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

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m², 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, see the CDC website: [https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html](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.
FAQs (cont’d)

Clinical trials

? How can I register my patients for a clinical trial with REGEN-COV for COVID-19?

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

? Is REGEN-COV being studied in ongoing clinical trials?

Please refer to Appendix C of this guidebook for more information. Clinical investigators, hospitals, or clinical sites interested in joining the REGEN-COV clinical program can email Regeneron at COVID19SitelInterest@regeneron.com.
APPENDIX E:

Basic equipment recommendations
Equipment requirements may vary by state. Follow your local requirements when determining the equipment needed for your treatment setting. Based on Regeneron’s clinical trial experience, the following equipment should be considered to ensure the most optimal care environment for patients receiving REGEN-COV. This list is not intended to substitute for your independent medical judgment.

**Basic equipment recommendations**

### Basic Equipment Recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPE</strong></td>
<td>Gloves, Gowns, Eye and face protection (e.g., goggles, safety glasses, face shields), NIOSH-certified, disposable N95 filter facepiece respirators or better</td>
</tr>
<tr>
<td><strong>Infusion supplies</strong></td>
<td>Infusion chairs – recommended only, IV pole, Administration set, IV and catheters, Infusion pumps (if available), Infusion pump bracket for IV pole (if available), 3-mL saline syringes, Appropriately sized syringes, Alcohol wipes, 2x2 gauze pads, Adhesive bandages, Occlusive dressing, Absorbent underpads (blue pads), Extension set tubing, 18-gauge stainless steel needles, Sharps containers, Tape, Transilluminator (vein finder)</td>
</tr>
<tr>
<td><strong>Injection supplies</strong></td>
<td>3-mL or 5-mL polypropylene Luer lock syringes with Luer connection, 21-gauge 1.5-inch transfer needles, 25-gauge or 27-gauge needle for subcutaneous injection</td>
</tr>
<tr>
<td><strong>General supplies</strong></td>
<td>Infusion reaction kit, Vital signs equipment, Reaction management kit, IV diphenhydramine, IV corticosteroid (e.g., methylprednisolone 125 mg), epinephrine (auto-injector preferred), CPR barrier mask and bag valve mask, oxygen and delivery devices (nasal cannula and non-rebreather mask), Locking refrigerator with temperature monitoring capability, Privacy screens, Biohazard disposal bag, Disposable disinfecting wipes, Thermometer probe covers (if required), 70% alcohol wipes, Paper towels, Trash bins and liners</td>
</tr>
</tbody>
</table>

Additional information on administration sets can be found in Section 6 of this guidebook.