Casirivimab and imdevimab are investigational therapies and have been authorized by FDA for the emergency use described below. Casirivimab and imdevimab must be administered together. Casirivimab and imdevimab are not FDA approved for any use. Safety and effectiveness of casirivimab and imdevimab have not been fully established for the treatment of COVID-19.

The Secretary of the Department of Health and Human Services has declared a public health emergency that justifies the emergency use of the unapproved products, 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 progressing to severe COVID-19 and/or hospitalization. In response, the US Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for casirivimab and imdevimab, in the treatment of COVID-19. [see Limitations of Use]

• 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 casirivimab and imdevimab 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

• Casirivimab and imdevimab are not authorized for use in patients:
  – who are hospitalized due to COVID-19, OR
  – who require oxygen therapy due to COVID-19, OR
  – who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

• Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19

BE SURE TO CHECK REGENCOV2.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 casirivimab and imdevimab

Casirivimab and imdevimab administered together by intravenous infusion, also known as REGN10933 and REGN10987, respectively, form a dual monoclonal antibody (mAb) therapy cocktail designed specifically to block infectivity of SARS-CoV-2, the virus that causes COVID-19.

To develop casirivimab and imdevimab, 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 antibodies that form casirivimab and imdevimab bind noncompetitively to the critical receptor-binding domain of the virus’s spike protein. In preclinical studies, each variant of the virus showing reduced susceptibility to one mAb retained susceptibility to the other, and all variants retained susceptibility to the casirivimab + imdevimab combination. There is, however, a potential risk of treatment failure due to the development of viral variants that are resistant to the casirivimab + imdevimab combination.

The development and manufacturing of casirivimab and imdevimab 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 US Department of Health and Human Services under OT number: HHSO100201700020C.

The casirivimab and imdevimab antibody cocktail continues to be evaluated in Phase 2/3 clinical trials for the treatment of COVID-19 in certain hospitalized and nonhospitalized patients, the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK, and a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals. As of November 2020, more than 7000 people have participated in casirivimab and imdevimab clinical trials. For information on these ongoing trials, visit www.clinicaltrials.gov. Casirivimab and imdevimab do not have FDA Emergency Use Authorizations in these populations described and are not FDA approved for these uses.
About casirivimab and imdevimab

This Casirivimab and Imdevimab EUA Guidebook compiles critical information, including Regeneron’s clinical trial experience with casirivimab and imdevimab, 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 casirivimab and imdevimab 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 PROFESSIONALS
POPULATION FOR ANTIBODY TREATMENT

Authorized Use and Important Information for Healthcare Providers
Casirivimab and imdevimab are investigational therapies and have been authorized by FDA for the emergency use described below. Casirivimab and imdevimab must be administered together. Casirivimab and imdevimab are not FDA approved for any use. Safety and effectiveness of casirivimab and imdevimab have not been fully established for the treatment of COVID-19.

The Secretary of the Department of Health and Human Services has declared a public health emergency that justifies the emergency use of the unapproved products, 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 progressing to severe COVID-19 and/or hospitalization. In response, the US Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for casirivimab and imdevimab, in the treatment of COVID-19. [see Limitations of Use]

• 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 casirivimab and imdevimab 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
• Casirivimab and imdevimab are not authorized for use in patients:
  – who are hospitalized due to COVID-19, OR
  – who require oxygen therapy due to COVID-19, OR
  – who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

• Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19

REGENERON | 6
This Emergency Use Authorization (EUA) is for the use of the unapproved products, casirivimab and imdevimab, 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 progressing to severe COVID-19 and/or hospitalization [see Limitations of Authorized Use].

HIGH RISK IS DEFINED AS PATIENTS WHO MEET AT LEAST ONE OF THE FOLLOWING CRITERIA:

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

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

Healthcare providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS potentially related to casirivimab and imdevimab. See sections 8 and 9 of the Full EUA Prescribing Information for reporting requirements.

- The authorized dosage is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset
- Casirivimab and imdevimab solutions must be diluted prior to administration

(continued on next page)
Additional Information for Healthcare Providers:

- Casirivimab and imdevimab carton and vial labels may instead be labeled REGN10933 and REGN10987, respectively.

- You may receive cartons and vials of casirivimab and imdevimab that are labeled “for intravenous infusion or subcutaneous injection.” However, casirivimab and imdevimab must be administered together (although packaged separately) after dilution by intravenous infusion only.

- Store casirivimab and imdevimab together in inventory. See www.regencov2.com/access for images of packaging.

- Casirivimab and imdevimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- The recommended dose is 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion over at least 60 minutes as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Since the optimal dosing regimen has not yet been established, it might be updated as new data become available. See the Fact Sheet for Healthcare Providers for complete dosage, preparation, and administration instructions.
• The prescribing healthcare provider and/or the provider’s designee are responsible for mandatory reporting of all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to casirivimab and imdevimab. 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 using a postage-paid Form FDA 3500 and returning by mail/fax or by calling 1-800-FDA-1088 to request a reporting form.** In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc. via fax or email.
Casirivimab and imdevimab are unapproved investigational therapies, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use.

• **Warnings and Precautions:**
  - **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Infusion-related reactions have been observed with administration of casirivimab and imdevimab. Signs and symptoms of infusion related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and/or dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

- **Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19:** Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab are not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

• **Adverse Reactions:**
  - Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the casirivimab and imdevimab 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab 8,000 mg group and 6 (2.3%) patients in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia and hypoxia (placebo). **Casirivimab and imdevimab are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).**

- One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000 mg dose
of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved.

- **Patient Monitoring Recommendations:** Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

- **Use in Specific Populations:**
  - **Pregnancy:** There is currently limited clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are pregnant. Casirivimab and imdevimab therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.
  
  - **Nursing Mothers:** There is currently no clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are breastfeeding. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for casirivimab and imdevimab and any potential adverse effects on the breastfed child from casirivimab and imdevimab or from the underlying maternal condition.
SECTION 2:
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 casirivimab and imdevimab 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 US Department of Health and Human Services. Regeneron expects to have casirivimab and imdevimab treatment doses ready for approximately 80,000 patients by the end of November 2020, approximately 200,000 patients by the first week of January 2021, and approximately 300,000 patients by the end of January 2021.

As part of Operation Warp Speed, the US government and Regeneron have signed an agreement for this initial supply of casirivimab and imdevimab. The US government is coordinating with state authorities to allocate the antibody cocktail on a weekly basis based on the number of COVID-19 cases in each state. Regeneron will ship casirivimab and imdevimab to AmerisourceBergen, a national distributor, which will distribute the therapy as directed by the government.

Regeneron continues to increase in-house production of casirivimab and imdevimab, and the company has partnered with Roche to increase the global supply beginning in 2021. If the therapy proves effective in clinical trials and regulatory approvals are granted, Regeneron will manufacture and distribute it in the US and Roche will develop, manufacture, and distribute it outside the US. Once both companies are at full manufacturing capacity in 2021, at least 2 million treatment doses are expected to be available annually.

Be sure to visit www.REGENCOV2.com for periodic updates.
SECTION 3: ALLOCATION, ORDERING, AND ADMINISTRATION SITES
How can infusion sites order casirivimab and imdevimab?
Casirivimab and imdevimab are being allocated and therefore cannot be ordered through a wholesaler. AmerisourceBergen will proactively contact infusion sites that have received State Health Department allocations to confirm acceptance of the allocation. Product allocations will occur and quantities may fluctuate depending on the medical need. Infusion sites should contact their state health departments to discuss any allocation of casirivimab and imdevimab for their site(s).

What are the administration sites for casirivimab and imdevimab?
Casirivimab and imdevimab will initially be made available to sites through the direction of state or territory health departments. Hospitals, ambulatory centers, and other administration sites that are interested in ordering casirivimab and imdevimab should contact their state or territory health departments to discuss any allocation of casirivimab and imdevimab for their site(s).

How will casirivimab and imdevimab be shipped?
Upon acceptance of the allocation, sites of care will have the product shipped to them by AmerisourceBergen. These shipments will contain refrigerated (2-8 °C) product. The product volume is 24 cartons per shipper box, and 162 shipper boxes per pallet. Product is available in 4 different shipping sizes: Small contains 64 cartons; Medium contains 144 cartons, Large contains 200 cartons, and Extra Large contains 454 cartons.

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**ALLOCATION, ORDERING, AND ADMINISTRATION SITES**

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SECTION 4:
CODING AND REIMBURSEMENT
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 casirivimab and imdevimab Therapy and Administration:

• Review of Relevant Codes
  – ICD-10-CM Diagnosis Codes
  – Level I HCPCS CPT Codes
  – Level II HCPCS Product Codes
  – NDC

• Additional considerations

Review of relevant codes
The following codes should be confirmed with each respective payer, as there may be variability in both coding and documentation requirements.
International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes

A COVID-19 diagnosis code was implemented for services on or after April 2, 2020. This code should be designated as the primary diagnosis. Providers will select secondary diagnoses based on the patient presentation of further complications from COVID-19. These complications require appropriate documentation in the patient’s medical record.

<table>
<thead>
<tr>
<th>Code</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>


Casirivimab and imdevimab will be administered via a single intravenous infusion. Please check with the payer to determine the appropriate administration code.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0243</td>
<td>Intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring</td>
</tr>
</tbody>
</table>


CODING AND REIMBURSEMENT (CONT’D)

Level II Healthcare Common Procedure Coding System (HCPCS) Drug Coding

The following HCPCS code may be used to identify casirivimab and imdevimab. Please check with the payer to determine the appropriate drug code.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q0243</td>
<td>Injection, casirivimab and imdevimab, 2400 mg</td>
</tr>
</tbody>
</table>

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

- Treatment NDCs
- Descriptor of antibody name(s)
- Mode of administration

Casirivimab and Imdevimab National Drug Codes (NDC)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Concentration</th>
<th>Package size</th>
<th>NDC number</th>
</tr>
</thead>
<tbody>
<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></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></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.

*Note that each NDC code has been “zero-filled” to ensure creation of an 11-digit code that meets HIPAA compliant standards. The zero-fill location is indicated in bold. HIPAA (Health Insurance Portability and Accountability Act); NDC (National Drug Code).


CODING AND REIMBURSEMENT (CONT’D)

Additional Considerations

Since casirivimab and imdevimab 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.

For Medicare beneficiaries, providers must report the applicable drug HCPCS code and appropriate units with a token charge of less than $1.01 for the item in the covered charge field and mirror this less than $1.01 amount reported in the noncovered charge field. Providers must also bill the corresponding drug administration charge with the appropriate drug administration CPT code.6

SECTION 5:
PRODUCT PACKAGING
PRODUCT PACKAGING

IMPORTANT PACKAGING INFORMATION

Casirivimab and imdevimab carton and vial labels may instead be labeled REGN10933 and REGN10987, respectively.

You may receive cartons and vials of casirivimab and imdevimab that are labeled “for intravenous infusion or subcutaneous injection.” However, casirivimab and imdevimab must be administered together (although packaged separately) after dilution by intravenous infusion only.

• REGN10933 or casirivimab; these refer to the same antibody
• REGN10987 or imdevimab; these refer to the same antibody

Each antibody will arrive in an individual package and both must be administered in the proper total volume to constitute a therapeutic dose of casirivimab and imdevimab.
CASIRIVIMAB AND IMDEVIMAB PACKAGING EVOLUTION

You may encounter variations in the packaging and vial labeling of casirivimab and imdevimab. This is because some clinical trial supply is being made available to fulfill need during this public health emergency.

<table>
<thead>
<tr>
<th>Vial</th>
<th>Carton</th>
<th>Vial</th>
<th>Carton</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>1332 mg/11.1 mL (120 mg/mL solution)</td>
<td>1B</td>
<td>1332 mg/11.1 mL (120 mg/mL solution)</td>
</tr>
<tr>
<td>2A</td>
<td>300 mg/2.5 mL (120 mg/mL solution)</td>
<td>2B</td>
<td>300 mg/2.5 mL (120 mg/mL solution)</td>
</tr>
</tbody>
</table>
Casirivimab and imdevimab must be administered together although they are packaged separately.

1A, 1B, 2A, 2B do not include expiration on packages. To obtain expiration dating contact Regeneron Medical Information at medical.information@regeneron.com

1A, 1B, 2A, 2B, 3A, 3B, 3C, 3D top panels as illustrated were modified for readability. The text on the actual packages will be inverted.

*Casirivimab and imdevimab must be administered together although they are packaged separately.

FOR INFORMATION ABOUT THE DOSING AND ADMINISTRATION OF CASIRIVIMAB AND IMDEVIMAB, SEE SECTION 6 AND APPENDIX A OF THIS GUIDEBOOK.
SECTION 6:

PREPARATION AND ADMINISTRATION INSTRUCTIONS
PREPARATION AND ADMINISTRATION INSTRUCTIONS

Dosing and Administration

• The optimal dosing regimen for treatment of COVID-19 has not yet been established
• The recommended dosing regimen may be updated as data from clinical trials become available
• **CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER (ALTHOUGH PACKAGED SEPARATELY) AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY**
  
• Casirivimab and imdevimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary

• The recommended dose is 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single IV infusion over at least 60 minutes as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.
  
See the **Fact Sheet for Healthcare Providers** for complete dosage, preparation, and administration instructions

• No dose adjustment is recommended in pregnant or lactating women, pediatric patients who weigh at least 40 kg, or patients with renal impairment
  
○ **Pregnancy:** There is currently limited clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are pregnant. Casirivimab and imdevimab therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus

○ **Nursing Mothers:** There is currently no clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are breastfeeding. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for casirivimab and imdevimab and any potential adverse effects on the breastfed child from casirivimab and imdevimab or from the underlying maternal condition
PREPARATION AND ADMINISTRATION INSTRUCTIONS (CONT’D)

Storage and handling of prepared dosages

Casirivimab is preservative-free. Discard any unused portion.

Imdevimab is preservative-free. Discard any unused portion.

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

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

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 2-8 °C (36-46 °F) for no more than 36 hours and at room temperature up to 25 °C (77 °F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.*

*CARTONS AND VIALS FOR CASIRIVIMAB AND IMDEVIMAB MAY BE LABELED REGN10933 AND REGN10987, RESPECTIVELY.

*These times were based on preparation in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> pharmacy standards for compounding sterile products. 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

PREPARATION

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

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

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

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

3. Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride.

4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial* using two separate syringes and dilute together in the infusion bag containing 0.9% Sodium Chloride, see Table 2. Discard any product remaining in the vial.

5. Gently invert infusion bag by hand approximately 10 times to mix. Do not shake.

This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2-8 °C (36-46 °F) for no more than 36 hours and at room temperature up to 25 °C (77 °F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.†

*Multiple vials may be needed to obtain 10 mL. See preparation and administration instructions on the next page.
†These times were based on preparation in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> pharmacy standards for compounding sterile products.
PREPARATION AND ADMINISTRATION INSTRUCTIONS (CONT’D)

Table 1: Vial combinations available for casirivimab REGN10933 and imdevimab REGN10987

<table>
<thead>
<tr>
<th>Combinations available</th>
<th>Number of vials needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vial of casirivimab 11.1 mL AND 1 vial of imdevimab 11.1 mL</td>
<td>2</td>
</tr>
<tr>
<td>4 vials of casirivimab 2.5 mL AND 4 vials of imdevimab 2.5 mL</td>
<td>8</td>
</tr>
<tr>
<td>1 vial of casirivimab 11.1 mL AND 4 vials of imdevimab 2.5 mL</td>
<td>5</td>
</tr>
<tr>
<td>4 vials of casirivimab 2.5 mL AND 1 vial of imdevimab 11.1 mL</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2: Casirivimab and imdevimab for IV Infusion (to be administered together as a 2400-mg dose)*

<table>
<thead>
<tr>
<th>Antibody dose</th>
<th>Volume to withdraw from vial</th>
<th>Number of vials needed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casirivimab</td>
<td>10 mL</td>
<td>1 vial of 11.1 mL OR 4 vials of 2.5 mL</td>
</tr>
<tr>
<td>REGN10933 1200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imdevimab</td>
<td>10 mL</td>
<td>1 vial of 11.1 mL OR 4 vials of 2.5 mL</td>
</tr>
<tr>
<td>REGN10987 1200 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: casirivimab=REGN10933; imdevimab=REGN10987.
*1200 mg of casirivimab and 1200 mg of imdevimab are to be administered together as a single intravenous infusion for a combined 2400 mg dose.
*One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.
PREPARATION AND ADMINISTRATION INSTRUCTIONS (CONT’D)

Administration

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 IV bag

• Prime the infusion set

• Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter. See Table 3.

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

• After infusion is complete, flush residual volume from tubing with 0.9% Sodium Chloride Injection to ensure patient receives entire dose

• Discard unused product

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

*If alternate materials are used, the compatibility of these materials should be confirmed with that vendor. Casirivimab and imdevimab have no known incompatibilities with conventional medical supplies and equipment.

Table 3: Gravity drip rate

<table>
<thead>
<tr>
<th>VTBI (mL)</th>
<th>Duration (minutes)</th>
<th>Drop Factor (drops per mL)</th>
<th>Drops per minute</th>
<th>Drops per 15 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>60</td>
<td>10 gtt/mL</td>
<td>42 gtt/min</td>
<td>11 drops per 15 seconds</td>
</tr>
<tr>
<td>250</td>
<td>60</td>
<td>12 gtt/mL</td>
<td>50 gtt/min</td>
<td>13 drops per 15 seconds</td>
</tr>
<tr>
<td>250</td>
<td>60</td>
<td>15 gtt/mL</td>
<td>63 gtt/min</td>
<td>16 drops per 15 seconds</td>
</tr>
<tr>
<td>250</td>
<td>60</td>
<td>20 gtt/mL</td>
<td>83 gtt/min</td>
<td>21 drops per 15 seconds</td>
</tr>
<tr>
<td>250</td>
<td>60</td>
<td>60 gtt/mL</td>
<td>250 gtt/min</td>
<td>63 drops per 15 seconds</td>
</tr>
</tbody>
</table>

SECTION 7:
EDUCATION AND AWARENESS
EDUCATION AND AWARENESS

How SARS-CoV-2 works

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

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

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

ACE2, angiotensin-converting enzyme 2. RBD, receptor-binding domain.
EDUCATION AND AWARENESS (CONT’D)

SARS-CoV-2 replicates within host cells to form new virus particles

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. Some RNA is translated into proteins by the cell’s machinery.
4. Some of these proteins form a replication complex to make more viral RNA.
5. Proteins and 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 respiratory routes of host-to-host transmission:

- Airborne aerosols
  - Respiratory droplets >5 µm diameter
  - Droplets travel ≤1 m
- Direct contact
- Surface contact
- Indirect contact
- Fecal-oral

FOR MORE INFORMATION ABOUT SARS-CoV-2, VISIT WWW.REGENCOV2.COM
Like vaccines, antiviral monoclonal antibodies may help people with SARS-CoV-2

How antiviral monoclonal antibodies and vaccines compare and how both may help against COVID-19

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 dangerous invaders.

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.

Antibodies are Y-shaped proteins produced by the human body as part of a normal immune response to foreign molecules. Antibodies help fight off foreign substances before they can cause sickness.

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.
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’re born with. But the immunity you gain during your lifetime is called **adaptive immunity**, and it has two 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

Develops immediately after receiving exogenous antibodies from an injection, infusion, or blood transfer.

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 antibodies outside of the body—corresponding to specific virus-neutralizing antibodies similar to those that would be elicited by a vaccine or exposure to the virus itself.

EXOGENOUS ANTIBODIES ARE:

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

These antibodies are then:

- Put into a cell line that can produce the desired 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 two antibodies against a pathogen combined in a single medicine. The different antibodies working in slightly different ways have a higher chance of neutralizing the virus.

THIS ANTIVIRAL ANTIBODY MEDICINE IS GIVEN:

As treatment: For sick patients through IV to block active infection.

With this approach, immunity is provided immediately but is temporary.
Antibodies block ability to bind and infect ACE2 receptor.

Virus binds to receptor to infect healthy cells.

Spike protein

Antibodies neutralize the SARS-CoV-2 virus with an antibody combination.

Antibodies block ability to bind and infect.
ACTIVE IMMUNITY

Develops over time in response to an infection or vaccination.

VACCINES

Used to induce the body’s active immune response in order to protect from an infectious viral disease, such as measles, the flu, or coronaviruses like COVID-19.

A weakened, or attenuated, virus.

A dead, or inactivated, form of the virus.

A fragment of the virus.*

The virus’s RNA or DNA.*

*These two approaches are primarily being explored for COVID-19.

To make many doses of vaccines, manufacturers:

- Gather needed key ingredients.
- Produce the antigen in large quantities.
- Package the antigen into an injection-ready form.

VACCINES WORK BY:

Exposing healthy patients to one of the items above via injection, which tricks the immune system into thinking it is infected and generating a response.

B cells begin producing protective antiviral antibodies in response.

With time, active immunity is acquired.

Immunity is delayed but usually lasts for a longer amount of time. Experts don’t yet know how long active immunity will last against COVID-19. Vaccines are not intended to treat people with active infections.
**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 also risks to both approaches, and healthcare providers and patients should weigh out the benefits and risks of both.

**ANTIVIRAL MONOCLONAL ANTIBODIES could serve as an important option. They may have utility for certain people, such as those who are immunocompromised, those with active infections, or those who do not respond to a vaccine. These approaches are important to address the COVID-19 pandemic.**

Learn more about Regeneron’s Antiviral Monoclonal Antibodies, technologies, and COVID-19 research at regeneron.com/covid19.

**TO LEARN MORE ABOUT PASSIVE vs ACTIVE IMMUNITY, VISIT WWW.REGENCOV2.COM**
SECTION 8:
CLINICAL DATA
Casirivimab and Imdevimab Clinical Trials

The data supporting the casirivimab and imdevimab EUA are based on the analysis of Phase 1/2 from trial R10933-10987-COV-2067 that occurred after 799 enrolled subjects had completed at least 28 days of study duration. R10933-10987-COV-2067 is a randomized, double-blinded, placebo-controlled clinical trial studying casirivimab and imdevimab for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized).

Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200 mg of each) (N=266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (N=267), or placebo (N=266).
**PATIENT POPULATION:**
- Adult, nonhospitalized COVID-19 patients with at least 1 or more COVID-19 symptoms that were at least mild in severity
- SARS-CoV-2 confirmed by molecular testing ≤ 72 hours from randomization
- Symptom onset ≤ 7 days from randomization
- Not under any current medication used/indicated to treat COVID-19

**SCREENING**
- Confirmation of SARS-CoV-2 infection and COVID-19 symptom evaluation
- Randomization
- IV infusion

**FOLLOW UP**
- Daily electronic clinical outcome assessment (eCOA)
- Collection of SAE/AESI, con meds, and medically attended visits

- ▶️ = NP swabs
- ▶️ = Biomarkers and NP swabs
- ▼️ = Biomarkers (Phase 1 only in this data cut) and NP swabs

**Day 1**
- Baseline

**Day 3, 5, 7, 15**

**Day 18, 22, 25, 29**
- End of study

*Serum for PK (Day 3, 5, 7, 15 included in Phase 1 only).*

**CLINICAL DATA (CONT’D)**

2067 nonhospitalized seamless phase 1/2/3 study design for two analysis sets
Median age was 42 years (with 7% of subjects ages 65 years or older)
53% of subjects were female
85% white
50% Hispanic or Latino
9% Black
34% were considered high risk
Approximately 31% of subjects reported at least 1 severe symptom at baseline
36% reported at least 1 moderate symptom and no severe symptoms
13% reported only mild symptoms
Median duration of symptoms was 3 days
Mean viral load was 5.8 log_{10} copies/mL at baseline

The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The prespecified primary endpoint in Phase 1/2 of trial R10933-10987-COV-2067 was the time-weighted average (TWA) change from baseline in viral load (log_{10} copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, in subjects with a positive baseline RT-qPCR value, ie, the modified full analysis set (mFAS).

In the mFAS (n=665) for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo was -0.36 log_{10} copies/mL (P<0.0001). The largest reductions in viral load relative to placebo occurred in patients with high viral load (-0.78 log_{10} copies/mL) or who were seronegative (-0.69 log_{10} copies/mL) at baseline. Reductions occurring from Day 1 through Day 11 were similar to those for Day 1 through Day 7. Figure 1 shows the mean change from baseline in SARS-CoV-2 viral load over time.
While viral load was used to define the primary endpoint in the Phase 1/2 analysis, clinical evidence demonstrating that casirivimab and imdevimab may be effective came from the predefined secondary endpoint, medically attended visits (MAV) related to COVID-19. Medically attended visits comprised hospitalizations, emergency room visits, urgent care visits, or physician office/telemedicine visits for COVID-19. A lower proportion of subjects treated with casirivimab and imdevimab had COVID-19–related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with casirivimab and imdevimab had COVID-19–related hospitalizations or emergency room visits compared to placebo, see Table 1.

Results for this endpoint were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for casirivimab and imdevimab compared to placebo was greater in subjects at high risk for progression to severe COVID-19 and/or hospitalization, according to the criteria outlined (Table 2).

The authorized dosage in adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes.
**Table 1: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits Within 28 Days After Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Events</th>
<th>Proportion of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>231</td>
<td>10</td>
<td>4%</td>
</tr>
<tr>
<td>2400 mg casirivimab and imdevimab</td>
<td>215</td>
<td>4</td>
<td>2%</td>
</tr>
<tr>
<td>8000 mg casirivimab and imdevimab</td>
<td>219</td>
<td>4</td>
<td>2%</td>
</tr>
<tr>
<td>All doses casirivimab and imdevimab</td>
<td>434</td>
<td>8</td>
<td>2%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hospitalization and emergency room visits were a subset of a key secondary endpoint, medically attended visits, which also included urgent care visits, physician’s office visits, and telemedicine visits.

<sup>b</sup> N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization.

<sup>c</sup> 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab).

<sup>d</sup> 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab).

---

**Table 2: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits Within 28 Days After Treatment for Subjects at Higher Risk of Hospitalization**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Events</th>
<th>Proportion of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>78</td>
<td>7</td>
<td>9%</td>
</tr>
<tr>
<td>2400 mg casirivimab and imdevimab</td>
<td>70</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>8000 mg casirivimab and imdevimab</td>
<td>81</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>All doses casirivimab and imdevimab</td>
<td>151</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hospitalization and emergency room visits were a subset of a key secondary endpoint, medically attended visits, which also included urgent care visits, physician’s office visits, and telemedicine visits.

<sup>b</sup> N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization.

<sup>c</sup> 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab).

<sup>d</sup> 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab).

The median time to symptom improvement, as recorded in a trial-specific daily symptom diary, was 5 days for casirivimab and imdevimab-treated subjects, as compared with 6 days for placebo-treated subjects. Symptoms assessed were shortness of breath or difficulty breathing, chills, feverish, sore throat, cough, nausea, vomiting, diarrhea, headache, red or watery eyes, body and muscle aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum/phlegm, runny nose. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild at baseline being scored as absent.
**Clinical Data (Cont’d)**

### Incidence of Key Safety Events for the 3 Treatment Groups

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>Placebo (n=93)</th>
<th>Casirivimab and Imdevimab Low Dose (2.4 g IV) (n=88)</th>
<th>Casirivimab and Imdevimab High Dose (8.0 g IV) (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment TEAE</td>
<td>4 (4.3%)</td>
<td>1 (1.1%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>SAE</td>
<td>2 (2.2%)</td>
<td>1 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related reactions Grade ≥2 thru Day 4</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Hypersensitivity reactions Grade ≥2 thru Day 29</td>
<td>2 (2.2%)</td>
<td>0</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to study infusion interruption</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

SAE=serious adverse events; TEAE=treatment-emergent adverse events.

- Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the casirivimab and imdevimab 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab 8,000 mg group and 6 (2.3%) patients in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia and hypoxia (placebo). Casirivimab and imdevimab are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

- One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved.

The authorized dosage in adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes.
WARNINGS AND PRECAUTIONS (CONT’D)

• Casirivimab and imdevimab are unapproved investigational therapies, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use.

- Hypersensitivity Including Infusion-Related Reactions: There is a potential for serious hypersensitivity reactions, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care. Infusion-related reactions have been observed with administration of casirivimab and imdevimab. Signs and symptoms of infusion-related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and/or dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

The authorized dosage in adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes.

- Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, casirivimab and imdevimab are not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non–COVID-19-related comorbidity.

FOR MORE CLINICAL DATA, VISIT WWW.REGENCOV2.COM TO VIEW THE ANTIVIRAL AND CLINICAL PROFILE OF CASIRIVIMAB AND IMDEVIMAB.
APPENDIX A:

DEAR HEALTHCARE PROVIDER LETTER:
IMPORTANT INFORMATION FOR HEALTHCARE PROVIDERS
IMPORTANT PRESCRIBING INFORMATION

Subject: Preventing Medication Errors with Casirivimab and Imdevimab

Dear Healthcare Provider:

This notice is to make you aware of the correct route of administration of casirivimab and imdevimab. Although they are packaged separately, **casirivimab and imdevimab must be administered together after dilution by single intravenous (IV) infusion only.**

Casirivimab and imdevimab are authorized\(^1\) for emergency use for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization. Healthcare Providers should administer casirivimab and imdevimab per the full Fact Sheet for Healthcare Providers available at [www.REGENCOV2.com](http://www.REGENCOV2.com).

**Casirivimab and Imdevimab Are Authorized ONLY for Intravenous Infusion after Dilution.**

You may receive cartons and vials of casirivimab and imdevimab that are labeled “for intravenous infusion or subcutaneous injection.” However, **casirivimab and imdevimab MUST be administered by INTRAVENOUS (IV) INFUSION ONLY** under this emergency use authorization. Healthcare providers should review the enclosed Fact Sheet for instructions on dosing, preparation and administration of casirivimab and imdevimab by intravenous infusion.

**Casirivimab and imdevimab must be administered together although they are packaged separately.**

There are three versions of casirivimab and imdevimab packaging, which are reproduced in the enclosure. Please note:

- Some cartons and vials of casirivimab and imdevimab may be instead labeled REGN10933 and REGN10987, respectively.
- Casirivimab and imdevimab may each be supplied as two different strengths: 1332 mg/11.1 mL single-dose vials and 300 mg/2.5 mL single-dose vials.
- One 11.1 mL vial of one antibody and four 2.5 mL vials of the other antibody can be used to create one treatment course.

\(^1\) Casirivimab and imdevimab are not approved, but The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products 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 and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization only for the duration of the declaration.
Regardless of the packaging, the 2 components, casirivimab and imdevimab, must be administered together as a single intravenous infusion. The route of administration authorized under the EUA is by intravenous infusion only after dilution.

**Healthcare Provider Action**

Healthcare providers should consider the following strategies in order to mitigate the risk of a possible medication error:

- Store casirivimab and imdevimab together in inventory.
- Create alerts in the electronic health record (EHR) systems for healthcare providers that casirivimab and imdevimab must be used together.
- Ensure that EHR systems always use casirivimab and imdevimab and only include an option for single IV infusion of casirivimab and imdevimab after dilution.

**Reporting Adverse Events and Medication Errors**

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

Under the Emergency Use Authorization, adverse events must be reported within 7 calendar days from the onset of the event. MedWatch adverse event reports can be submitted to FDA online at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm.
- Regular Mail or Fax: Download form https://www.accessdata.fda.gov/scripts/medwatch/index.cfm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

Healthcare providers must report all serious adverse events and medication errors when utilizing casirivimab and imdevimab to Regeneron at medical.information@regeneron.com.

The EUA Fact Sheet for Healthcare Providers is included with this notice, available at www.REGENCOV2.com, or available by scanning the QR Code below:

Johnathan Lancaster, MD
Vice President, Global Medical Affairs
Variations of the packaging and labeling of casirivimab and imdevimab

1a: casirivimab (also referred to as REGN10933) – 1332 mg/11.1 mL (120 mg/mL solution)

1b: imdevimab (also referred to as REGN10987) – 1332 mg/11.1 mL (120 mg/mL solution)
2a: casirivimab (also referred to as REGN10933) – 300 mg/2.5 mL (120 mg/mL solution)

Contains:
1 vial Solution of intravenous infusion or subcutaneous injection.
Administer in accordance with protocol instructions.
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.
Keep Out of Reach of Children. For Clinical Trial Use Only.

2b: imdevimab (also referred to as REGN10987) – 300 mg/2.5 mL (120 mg/mL solution)

Contains:
1 vial Solution of intravenous infusion or subcutaneous injection.
Administer in accordance with protocol instructions.
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.
Keep Out of Reach of Children. For Clinical Trial Use Only.

Caution: New Drug - Limited by Federal (or United States) law to investigational use.
Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA
Tel: +1 914-847-7000
3a: casirivimab (also referred to as REGN10933) – 300 mg/2.5 mL (120 mg/mL solution)

3b: casirivimab (also referred to as REGN10933) – 1332 mg/11.1 mL (120 mg/mL solution)
3c: imdevimab (also referred to as REGN10987) – 300 mg/2.5 mL (120 mg/mL solution)

3d: imdevimab (also referred to as REGN10987) – 1332 mg/11.1 mL (120 mg/mL solution)
CLINICAL TRIAL MODELING INFORMATION

Assuming the infusion site of care setup details provided below, this information can be used to model the estimated number of infusions (patients) an infusion site of care can serve, depending on its capacity.

Each infusion site of care will vary in terms of the number of chairs for infusion, staffing considerations, work-day length, and more. The information provided here is meant as a general guide based upon REGENERON’s clinical trial experience. In some cases, ideal criteria are included, such as for observation time. In other instances, such as the consent and intake time, there are estimated ranges shown, with “+” or “-” conditions in parentheses.

Casirivimab and Imdevimab must be administered together. If using prepared medication that is being refrigerated, allow the IV to equilibrate to room temperature (at least 30 minutes) prior to administration.

<table>
<thead>
<tr>
<th>ESTIMATED INFUSION TIMING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>Consent and intake time</td>
</tr>
<tr>
<td>IV prep time</td>
</tr>
<tr>
<td>Infusion time</td>
</tr>
<tr>
<td>Observation time</td>
</tr>
<tr>
<td><strong>TOTAL TIME</strong></td>
</tr>
</tbody>
</table>
APPENDIX C:
CURRENTLY ENROLLING CLINICAL TRIALS
Casirivimab and imdevimab are currently being studied in **two currently enrolling** Phase 2/3 clinical trials for the treatment of COVID-19 in certain hospitalized and outpatient ambulatory 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. **The use in these populations described here has not been granted an Emergency Use Authorization (EUA) and these uses are not approved by any regulatory authority.**

For more information on clinical trials testing the use of casirivimab and imdevimab, 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 patients</td>
<td>NCT04425629</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 2/3</td>
<td>Certain hospitalized adult patients</td>
<td>NCT04426695</td>
</tr>
<tr>
<td>Prevention</td>
<td>Phase 3</td>
<td>Prevention of SARS-CoV-2 infection in healthy adults who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay</td>
<td>NCT04452318</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase 3</td>
<td>Hospitalized patients (RECOVERY trial)</td>
<td>Not currently recruiting US patients</td>
</tr>
</tbody>
</table>

**FOR MORE CLINICAL TRIAL SITES, VISIT CLINICALTRIALS.GOV**
APPENDIX D:

FAQs
FAQs

FREQUENTLY ASKED QUESTIONS

What is an Emergency Use Authorization (EUA)?
An EUA allows the US 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 (FD&C 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.

How do casirivimab and imdevimab work?
Casirivimab and imdevimab are two noncompeting, virus-neutralizing antibodies that make up Regeneron’s investigational antibody therapy for the treatment of COVID-19.

Casirivimab and imdevimab bind simultaneously to different, non-overlapping epitopes on the severe acute respiratory syndrome 2 (SARS-CoV-2) spike (S) glycoprotein.

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 casirivimab and imdevimab. 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 using a postage-paid Form FDA 3500 and returning by mail/fax or by calling 1-800-FDA-1088 to request a reporting form. In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc. via fax (1-888-876-2736) or email (medical.information@regeneron.com).

Are there any warnings associated with the use of this combination therapy?
Casirivimab and imdevimab are unapproved investigational therapies, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with the combined use of casirivimab and imdevimab.
Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Infusion-related reactions have been observed with administration of casirivimab and imdevimab. Signs and symptoms of infusion-related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and/or dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab are not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

What adverse reactions have been identified thus far in the randomized trials? There are limited clinical data available for casirivimab and imdevimab. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use. Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the casirivimab and imdevimab 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab 8,000 mg group and 6 (2.3%) patients in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia and hypoxia (placebo). Casirivimab and imdevimab are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm.
FAQs (CONT’D)

These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved.

Who is eligible for treatment with unapproved products casirivimab and imdevimab under the EUA?
The combination of investigational casirivimab and imdevimab is authorized for use under an EUA for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Limitations of Authorized Use
- Casirivimab and imdevimab are not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

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.

Definition of high risk patients
High risk is defined as patients who meet at least one of the following criteria:
- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
FAQs (CONT’D)

• Are 12 – 17 years of age AND have
  ◦ BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
  ◦ sickle cell disease, OR
  ◦ congenital or acquired heart disease, OR
  ◦ neurodevelopmental disorders, for example, cerebral palsy, OR
  ◦ a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  ◦ asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

How can infusion sites order casirivimab and imdevimab?
Casirivimab and imdevimab are being allocated and therefore cannot be ordered through a wholesaler. AmerisourceBergen will proactively contact infusion sites that have received State Health Department allocations to confirm acceptance of the allocation. Product allocations will occur and quantities may fluctuate depending on the medical need. Infusion sites should contact their state health departments to discuss any allocation of casirivimab and imdevimab for their site(s).

How can I register my patients for a clinical trial with casirivimab and imdevimab for COVID-19?
For more information on clinical trials that are testing the use of casirivimab and imdevimab in COVID-19, please visit www.clinicaltrials.gov.

Are casirivimab and imdevimab being studied in ongoing clinical trials?
Clinical investigators, hospitals, or clinical sites interested in joining the casirivimab and imdevimab clinical program can email Regeneron at COVID19SitelInterest@regeneron.com
Equipment requirements may vary by state. Follow your local requirements when determining the equipment needed for your infusion center. Based on Regeneron's clinical trial experience, the following equipment should be considered to ensure the most optimal care environment for patients receiving casirivimab and imdevimab. This list is not intended to substitute for your independent medical judgment.

**BASIC EQUIPMENT RECOMMENDATIONS**

**PPE**
- Gloves
- Gowns
- Eye and face protection (e.g., goggles, safety glasses, face shields)
- NIOSH-certified, disposable N95 filter facepiece respirators or better

**Infusion supplies**
- Infusion chairs – recommended only
- IV pole
- Administration set
  - Sterile in-line 0.2/0.22 micron filter (may be integrated into administration set or separate add-on device)
- IV and catheters
- Infusion pumps (if available)
- 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)

**General supplies**
- 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

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