

November 21, 2020

Regeneron Pharmaceuticals, Inc.  
Attention: Yunji Kim, PharmD  
Director, Regulatory Affairs  
777 Old Saw Mill River Road  
Tarrytown, NY 10591

Dear Dr. Kim:

This letter is in response to Regeneron Pharmaceutical, Inc's ("Regeneron") request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of casirivimab and imdevimab, administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19), as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.<sup>1</sup> On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.<sup>2</sup>

Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication.

Based on review of the analysis of phase 1 and 2 data from the ongoing trial R10933-10987-COV-2067 (NCT04425629), a phase 1/2/3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of casirivimab and imdevimab 2400 mg IV or casirivimab and imdevimab 8000 mg IV or placebo in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that casirivimab and imdevimab, administered together, may be effective 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

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<sup>1</sup> U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.

<sup>2</sup> U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits of casirivimab and imdevimab, administered together, outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of casirivimab and imdevimab, to be administered together, for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

## **I. Criteria for Issuance of Authorization**

I have concluded that the emergency use of casirivimab and imdevimab for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that casirivimab and imdevimab, administered together, may be effective in treating 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, and that, when used under the conditions described in this authorization, the known and potential benefits of casirivimab and imdevimab outweigh the known and potential risks of such products; and
3. There is no adequate, approved, and available alternative to the emergency use of casirivimab and imdevimab, 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.<sup>3</sup>

## **II. Scope of Authorization**

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s)<sup>4</sup>, who will distribute to healthcare facilities or healthcare providers as

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<sup>3</sup> No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

<sup>4</sup> “Authorized Distributor(s)” are identified by Regeneron as an entity or entities allowed to distribute authorized casirivimab and imdevimab.

directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

- The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat 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;
- Casirivimab and imdevimab may only be administered together;
- Casirivimab and imdevimab is not authorized for use in the following patient populations<sup>5</sup>:
  - Adults or pediatric patients who are hospitalized due to COVID-19, or
  - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
- Casirivimab and imdevimab 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.
- The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

## Product Description

Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. Casirivimab and imdevimab are each supplied in individual single use vials. Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. For dilution, 20 mL of 0.9% Sodium Chloride Injection are withdrawn and discarded from the infusion bag, and 10 mL of casirivimab and 10 mL of imdevimab from each respective vial are transferred to the 0.9% Sodium Chloride Injection fusion bag.

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<sup>5</sup> 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.

The authorized casirivimab and imdevimab vial label and carton labeling may be clearly marked with either “Caution: New Drug- limited by Federal law (or United States) to Investigational use” or with “For use under Emergency Use Authorization (EUA)”. Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as “REGN10933” and “REGN10987”, respectively.

Casirivimab injection and imdevimab injection unopened vials should be stored under refrigerated temperature at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Diluted casirivimab and imdevimab infusion solution can be stored in the refrigerator between 2°C to 8°C (36°F to 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.

Casirivimab and imdevimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Regeneron’s website at [www.regencov2.com](http://www.regencov2.com):

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of casirivimab and imdevimab
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of casirivimab and imdevimab for Coronavirus Disease 2019 (COVID-19)
- Information Sheet (“Fact Sheet Directions”)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of casirivimab and imdevimab, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that casirivimab and imdevimab may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that casirivimab and imdevimab (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS’s determination under Section 564(b)(1)(C) described above and the Secretary of HHS’s corresponding declaration under Section 564(b)(1), casirivimab and imdevimab is authorized to treat mild to moderate COVID-19 illness 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, who

are at high risk for progressing to severe COVID-19 illness and/or hospitalization as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

### **III. Conditions of Authorization**

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

#### Regeneron and Company (Regeneron) and Authorized Distributors

- A. Regeneron and authorized distributor(s) will ensure that the authorized casirivimab and imdevimab is distributed as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.
- B. Regeneron and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.
- C. Regeneron and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized casirivimab and imdevimab. Regeneron will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).
- D. Regeneron may request changes to this authorization, including to the authorized Fact Sheets for casirivimab and imdevimab, that do not alter the analysis of benefits and risks that underlies this authorization and FDA may determine that such changes may be permitted without amendment of this EUA. That determination must be made by joint decision of the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research (CDER), the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER, and Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist/Office of the Commissioner.
- E. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized casirivimab and imdevimab that are reported to Regeneron using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal(SRP) as described on the [FDA SRP](#) web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the [FAERS electronic submissions](#) web page.

Submitted reports under both options should state: “Casirivimab and imdevimab treatment under Emergency Use Authorization (EUA).” For reports submitted under Option 1, include this language at the beginning of the question “Describe Event” for further analysis. For reports submitted under Option 2, include this language at the beginning of the “Case Narrative” field.

- F. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.
- G. Regeneron will submit information to the Agency within three working days of receipt of any information concerning any batch of casirivimab or imdevimab (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the product or its labeling to be mistaken for, or applied to, another article; and (2) information concerning any bacteriological or microscopic contamination, or any significant chemical, physical, or other change in deterioration in the product, or any failure of one or more batches of the product to meet the established specifications. Regeneron will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Regeneron must recall them.
- H. Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency.
- I. Regeneron will manufacture and test casirivimab and imdevimab per the process and methods, including in-process sampling and testing and finishing product testing (release and stability) to meet all specifications as detailed in Regeneron’s EUA request.
- J. Regeneron will list casirivimab and imdevimab with a unique product NDC for each presentation of each antibody under the marketing category of Unapproved Drug- Other. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.
- K. Through a process of inventory control, Regeneron and authorized distributor(s) will maintain records regarding distribution of the authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date).
- L. Regeneron and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom the Authorized Casirivimab and Imdevimab Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab

- M. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available

to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of casirivimab and imdevimab.

- N. Healthcare facilities and healthcare providers receiving casirivimab and imdevimab will track serious adverse events that are considered to be potentially attributable to casirivimab and imdevimab use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form ([www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call [1-800-FDA-1088](tel:1-800-FDA-1088) for questions. Submitted reports should state, “Casirivimab and imdevimab treatment under Emergency Use Authorization” at the beginning of the question “Describe Event” for further analysis.
- O. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.
- P. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).
- Q. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Regeneron and/or FDA. Such records will be made available to Regeneron, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

- R. All descriptive printed matter, advertising, and promotional materials relating to the use of the casirivimab and imdevimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.
- S. No descriptive printed matter, advertising, or promotional materials relating to the use of casirivimab and imdevimab may represent or suggest that such products are safe or effective when used 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.
- T. All descriptive printed matter, advertising, promotional material, relating to the use of the casirivimab and imdevimab clearly and conspicuously shall state that:
- the casirivimab and imdevimab has not been approved, but has been authorized for emergency use by FDA under an EUA, to treat 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.

- the emergency use of casirivimab and imdevimab is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

#### **IV. Duration of Authorization**

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton  
Chief Scientist  
Food and Drug Administration