

February 3, 2021

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

Dear Dr. Kim:

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 coronavirus disease 2019 (COVID-19).¹ 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.²

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of REGEN-COV (casirivimab and imdevimab, administered together)³ 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. 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.

On February 3, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the November 21, 2020 letter in its entirety with revisions incorporated to the product description of REGEN-COV reflecting that REGEN-COV will be packaged and distributed in dose pack bags. In addition, revisions have been incorporated to the condition on requesting changes to this authorization,

¹ 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.

² 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).

³ The November 21, 2020 EUA referred to the authorized product as “casirivimab and imdevimab, administered together”. Regeneron subsequently requested, and FDA concurred, that the authorized labeling be revised to add references to authorized products’ trade name, “REGEN-COV.” “REGEN-COV” is used in this February 3, 2021 reissued letter and denotes the use of casirivimab and imdevimab, administered together.

including changes to the authorized Fact Sheets, and new conditions have been incorporated relating to the development of instructional or educational materials as well as certain mandatory reporting requirements for healthcare facilities and providers.⁴ Lastly, updated safety information and details on possible side effects have been incorporated into the authorized Fact Sheets.

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 REGEN-COV 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 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 REGEN-COV 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 REGEN-COV 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 REGEN-COV 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 REGEN-COV 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 REGEN-COV outweigh the known and potential risks of such products; and
3. There is no adequate, approved, and available alternative to the emergency use of REGEN-COV 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.⁵

⁴ See conditions D, E, and S, respectively.

⁵ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

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 REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s)⁶, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;
- REGEN-COV 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;
- The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;
- REGEN-COV is not authorized for use in the following patient populations⁷:
 - 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.
- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- The use of REGEN-COV covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

⁶ “Authorized Distributor(s)” are identified by Regeneron as an entity or entities allowed to distribute authorized REGEN-COV.

⁷ Benefit of treatment with REGEN-COV 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.

REGEN-COV is available in dose pack bags that will include a sufficient number of vials of casirivimab and imdevimab to prepare one treatment dose.⁸ Casirivimab and imdevimab are each supplied in individual single use vials. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked “For Use under Emergency Use Authorization.” 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 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.

The dose pack bags containing unopened vials of casirivimab injection and imdevimab injection should be stored under refrigerated temperature at 2°C to 8°C (36°F to 46°F). The vials should be kept in the individual original cartons 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 or at room temperature up to 25°C (77°F) for no more than 4 hours.

REGEN-COV 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.REGENCOV.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 REGEN-COV, 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.

⁸ Individual vials of casirivimab and imdevimab distributed in interstate commerce prior to the reissuance of this letter remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of this authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either “Caution: New Drug - Limited by Federal (or United States) law 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.

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 REGEN-COV 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 REGEN-COV (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), REGEN-COV 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 REGEN-COV 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 REGEN-COV. 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 REGEN-COV. Any request for changes to this EUA must be submitted to the

Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.⁹

- E. Regeneron may develop instructional and educational materials to facilitate the emergency use of the authorized REGEN-COV (e.g., materials providing information on product administration and/or patient monitoring) under condition D of this letter of authorization.
- F. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized REGEN-COV 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: “REGEN-COV use for COVID-19 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.

- G. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.
- H. Regeneron will submit information to the Agency within three working days of receipt of any information concerning any batch of REGEN-COV (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 microbiological 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.
- I. Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control

⁹ The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency as described under condition D.

- J. 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.
- K. Regeneron will list the single dose pack bag containing casirivimab and imdevimab with a unique NDC from the NDCs of the single ingredient listings under the marketing category of Unapproved Drug-Other. As applicable, different vial sizes should be identified by a different package NDC within the product NDC. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at such establishment.
- L. 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).
- M. 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 REGEN-COV Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab

- N. 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 REGEN-COV.
- O. Healthcare facilities and healthcare providers receiving REGEN-COV will track serious adverse events that are considered to be potentially attributable to REGEN-COV 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), 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, “REGEN-COV use for COVID-19 under Emergency Use Authorization” at the beginning of the question “Describe Event” for further analysis.
- P. 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.
- Q. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGEN-COV (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).

- R. 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.
- S. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

- T. All descriptive printed matter, advertising, and promotional materials relating to the use of the REGEN-COV 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.
- U. No descriptive printed matter, advertising, or promotional materials relating to the use of REGEN-COV 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.
- V. All descriptive printed matter, advertising, promotional material, relating to the use of the REGEN-COV clearly and conspicuously shall state that:
 - REGEN-COV 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 REGEN-COV 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,

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration