scientific and academic experts, notify FDA of their intent to participate in the periodic stakeholder consultation meetings on MDUFA reauthorization. FDA believes that consistent stakeholder representation at these meetings will be important to ensure progress in these discussions. If you wish to participate in the stakeholder consultation meetings, please designate one or more representatives from your organization who will commit to attending these meetings and preparing for the discussions. Stakeholders who identify themselves through this notice, and are otherwise eligible to attend, may participate in all stakeholder consultation discussions while FDA negotiates with the regulated industry. These stakeholder discussions will satisfy the consultation requirement in section 738A(b)(3) of the FD&C Act.

II. Notification of Intent To Participate in Periodic Stakeholder Consultation Meetings

If you intend to participate in continued periodic stakeholder consultation meetings regarding MDUFA reauthorization, please provide notification by email to *MDUFAVReauthorization@fda.hhs.gov* by February 26, 2021. Your email should contain complete contact information, including name, title, affiliation, address, email address, phone number, and notice of any special accommodations required because of disability. Stakeholders will receive confirmation and additional information about the first meeting from FDA after the Agency receives this notification.

Dated: February 16, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021–03428 Filed 2–18–21; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2020–N–2305]

Authorizations of Emergency Use of Certain Drug and Biological Products During the COVID–19 Pandemic; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the issuance of five Emergency Use Authorizations (EUAs) (the Authorizations) under the Federal Food, Drug, and Cosmetic Act (FD&C Act) for drug and biological products for use during the COVID–19 pandemic. FDA issued one Authorization for a drug as requested by Baxter Healthcare Corporation (Baxter); one Authorization for a biological product as requested by the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services (ASPR/HHS); an Authorization for a drug and an Authorization for a biological product as requested by Eli Lilly and Company; and one Authorization for biological products as requested by Regeneron Pharmaceuticals, Inc. The Authorizations contain, among other things, conditions on the emergency use of the authorized products. The Authorizations follow the February 4, 2020, determination by the Secretary of HHS that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves a novel (new) coronavirus. The virus, now named SARS–CoV–2, causes the illness COVID–19. On the basis of such determination, the Secretary of HHS declared on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID–19 pandemic, pursuant to the FD&C Act, subject to the terms of any authorization issued under that section. The Authorizations, which include an explanation of the reasons for issuance, are reprinted in this document.

DATES: The Authorization for Baxter is effective as of August 13, 2020; the Authorization for ASPR/HHS is effective as of August 23, 2020; the Authorizations for Eli Lilly and Company are effective as of November 9, 2020, and November 19, 2020, respectively; and the Authorization for Regeneron Pharmaceuticals, Inc. is effective as of November 21, 2020.

ADDRESSES: Submit written requests for single copies of the EUAs to the Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4338, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your request or include a Fax number to which the Authorizations may be sent. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the Authorizations.

FOR FURTHER INFORMATION CONTACT: Michael Mair, Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4340, Silver Spring, MD 20993–0002, 301–796–8510 (this is not a toll free number).

SUPPLEMENTARY INFORMATION:

I. Background

Section 564 of the FD&C Act (21 U.S.C. 360bbb–3) allows FDA to strengthen the public health protections against biological, chemical, nuclear, and radiological agents. Among other things, section 564 of the FD&C Act allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product in certain situations. With this EUA authority, FDA can help ensure that medical countermeasures may be used in emergencies to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by biological, chemical, nuclear, or radiological agents when there are no adequate, approved, and available alternatives.

II. Criteria for EUA Authorization

Section 564(b)(1) of the FD&C Act provides that, before an EUA may be issued, the Secretary of HHS must declare that circumstances exist justifying the authorization based on one of the following grounds: (1) A determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents; (2) a determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to U.S. military forces, including personnel operating under the authority of title 10 or title 50, U.S. Code, of attack with (A) a biological, chemical, radiological, or nuclear agent or agents; or (B) an agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to U.S. military forces; [1] (3) a determination by the Secretary of HHS that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of U.S. citizens living

[1] In the case of a determination by the Secretary of Defense, the Secretary of HHS shall determine within 45 calendar days of such determination, whether to make a declaration under section 564(b)(1) of the FD&C Act, and, if appropriate, shall promptly make such a declaration.

abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents; or (4) the identification of a material threat by the Secretary of Homeland Security pursuant to section 319F–2 of the Public Health Service (PHS) Act (42 U.S.C. 247d–6b) sufficient to affect national security or the health and security of U.S. citizens living abroad.

Once the Secretary of HHS has declared that circumstances exist justifying an authorization under section 564 of the FD&C Act, FDA may authorize the emergency use of a drug, device, or biological product if the Agency concludes that the statutory criteria are satisfied. Under section 564(h)(1) of the FD&C Act, FDA is required to publish in the **Federal Register** a notice of each authorization, and each termination or revocation of an authorization, and an explanation of the reasons for the action. Section 564 of the FD&C Act permits FDA to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use when the Secretary of HHS has declared that circumstances exist justifying the authorization of emergency use. Products appropriate for emergency use may include products and uses that are not approved, cleared, or licensed under sections 505, 510(k), 512, or 515 of the FD&C Act (21 U.S.C. 355, 360(k), 360b, and 360e) or section 351 of the PHS Act (42 U.S.C. 262), or conditionally approved under section 571 of the FD&C Act (21 U.S.C. 360ccc). FDA may issue an EUA only if, after consultation with the HHS Assistant Secretary for Preparedness and Response, the Director of the National Institutes of Health, and the Director of the Centers for Disease Control and Prevention (to the extent feasible and appropriate given the applicable circumstances), FDA [2] concludes: (1) That an agent referred to in a declaration of emergency or threat can cause a serious or life-threatening disease or condition; (2) that, based on the totality of scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) The product may be effective in diagnosing, treating, or preventing (i) such disease or condition; or (ii) a serious or life-threatening disease or condition caused by a product authorized under section 564, approved or cleared under the FD&C Act, or licensed under section 351 of the PHS Act, for diagnosing, treating, or preventing such a disease or condition caused by such an agent; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product, taking into consideration the material threat posed by the agent or agents identified in a declaration under section 564(b)(1)(D) of the FD&C Act, if applicable; (3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition; (4) in the case of a determination described in section 564(b)(1)(B)(ii), that the request for emergency use is made by the Secretary of Defense; and (5) that such other criteria as may be prescribed by regulation are satisfied.

No other criteria for issuance have been prescribed by regulation under section 564(c)(4) of the FD&C Act.

III. The Authorizations

The Authorizations follow the February 4, 2020, determination by the Secretary of HHS that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves a novel (new) coronavirus. The virus, now named SARS–CoV–2, causes the illness COVID–19. Notice of the Secretary's determination was provided in the **Federal Register** on February 7, 2020 (85 FR 7316). On the basis of such determination, the Secretary of HHS declared on March 27, 2020, 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 FD&C Act, subject to the terms of any authorization issued under that section. Notice of the Secretary's declaration was provided in the **Federal Register** on April 1, 2020 (85 FR 18250). Having concluded that the criteria for issuance of the Authorizations under section 564(c) of the FD&C Act are met, FDA issued five authorizations for the emergency use of drug and biological products during the COVID–19 pandemic. On August 13, 2020, FDA issued an EUA to Baxter for REGIOCIT, subject to the terms of the Authorization. On August 23, 2020, FDA issued an EUA to ASPR/HHS for COVID–19 convalescent plasma, subject to the terms of the Authorization. On November 9, 2020, FDA issued an EUA to Eli Lilly and Company for bamlanivimab, subject to the terms of the Authorization (technical correction on November 10, 2020). On November 19, 2020, FDA issued an EUA to Eli Lilly and Company for OLUMIANT (baricitinib), for use in combination with VEKLURY (remdesivir), subject to the terms of the Authorization. On November 21, 2020, FDA issued an EUA to Regeneron Pharmaceuticals, Inc. for casirivimab and imdevimab, administered together, subject to the terms of the Authorization. The Authorizations, which are included after section IV of this document in their entirety (not including the authorized versions of the fact sheets and other written materials), provide an explanation of the reasons for issuance, as required by section 564(h)(1) of the FD&C Act. Any subsequent reissuances of these Authorizations can be found on FDA's web page: *https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.*

IV. Electronic Access

An electronic version of this document and the full text of the Authorizations are available on the internet at *https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.*

BILLING CODE 4164–01–P

[2] The Secretary of HHS has delegated the authority to issue an EUA under section 564 of the FD&C Act to the Commissioner of Food and Drugs.

August 13, 2020

Mr. Fortunato Aldape
Baxter Healthcare Corporation
Director, Global Regulatory Affairs, Acute Therapies
One Baxter Parkway
Deerfield, IL 60015

Dear Mr. Aldape:

This letter is in response to Baxter Healthcare Corporation's ("Baxter") request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for REGIOCIT replacement solution that contains citrate for regional citrate anticoagulation (RCA) of the extracorporeal circuit for emergency use as a replacement solution in adult patients treated with Continuous Renal Replacement Therapy (CRRT) and for whom RCA of the extracorporeal circuit is appropriate, in a critical care setting, during the Coronavirus Disease 2019 (COVID-19) pandemic, 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 Federal Food, Drug, and Cosmetic Act (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.[1] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, subject to the terms of the authorization issued under that section.[2]

The Agency has noted that SARS-CoV-2, the virus that causes COVID-19, has led to an increased population with critical illness and multiple organ failure, including acute kidney injury, increasing the need for CRRT. As a result, there is an insufficient supply of replacement solutions to meet the emergency need to provide CRRT in critically ill patients. Based on the totality of scientific evidence available, FDA has concluded that REGIOCIT may be effective for use as a replacement solution in adult patients treated with CRRT with suspected or confirmed

[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, 85 FR 7316 (February 7, 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).

COVID-19[3], and for whom RCA of the extracorporeal circuit is appropriate, in a critical care setting during the Coronavirus Disease 2019 (COVID-19) pandemic.

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 your REGIOCIT product, as described in the Scope of Authorization (Section II) of this letter, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of REGIOCIT, as described in the Scope of Authorization (Section II) of this letter, meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness and multiple organ failure, including acute kidney injury, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that REGIOCIT may be effective for use as a replacement solution in adult patients with suspected or known COVID-19[4] in a critical care setting who are being treated with CRRTand for whom RCA is appropriate, and that, when used under the terms and conditions described in this authorization, the known and potential benefits of REGIOCIT outweigh the known and potential risks of REGIOCIT; and

3. There is no adequate, approved, and available alternative to the emergency use of REGIOCIT due to an insufficient supply of FDA-approved alternatives to meet the emergency need during the COVID-19 pandemic.[5]

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:

- REGIOCIT will be used as a replacement solution only in adult patients being treated with CRRT and for whom RCA is appropriate.
- REGIOCIT will be administered only by a licensed healthcare provider in a critical care setting.

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[3] As noted in the letter of authorization, in the circumstances of this public health emergency, it would not be feasible to authorize REGIOCIT only to be used for patients with suspected or confirmed COVID-19; therefore, the authorization does not limit use to such patients.

[4] In the circumstances of this public health emergency, it would not be feasible to require healthcare providers to seek to limit REGIOCIT only to be used for patients with suspected or confirmed COVID-19; therefore, this authorization does not limit use to such patients.

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

- REGIOCIT will be available for use only in facilities that Baxter Healthcare Corporation has qualified[6] for receiving REGIOCIT.

REGIOCIT is a replacement solution that contains citrate for RCA of the extracorporeal circuit. REGIOCIT is authorized for emergency use as a replacement solution in adult patients treated with CRRT, and for whom RCA is appropriate, during the COVID-19 pandemic. REGIOCIT is intended for use in a critical care setting. REGIOCIT is intended to be used in continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodiafiltration (CVVHDF) modalities.

Authorized Product Details

REGIOCIT is supplied as a 5000 mL sterile solution of 0.503% sodium chloride and 0.529% sodium citrate in water for injection in a polyolefin clear plastic bag.

REGIOCIT is authorized under the terms and conditions of this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

REGIOCIT is authorized to be accompanied by the following product-specific information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Providers: Emergency Use of REGIOCIT during the COVID-19 Pandemic
- REGIOCIT Package Insert- EUA
- Fact Sheet for Patients and Caregivers: Emergency Use of REGIOCIT during the COVID-19 Pandemic

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 REGIOCIT, when used consistent within the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of REGIOCIT.

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 REGIOCIT may be effective for the uses described within the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that REGIOCIT, when used as described in the Scope of Authorization of this letter (Section II), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

[6] Baxter Healthcare Corporation will determine whether an individual facility is qualified, for the purposes of receiving REGIOCIT, in accordance with the process and criteria submitted in Baxter's EUA request.

The emergency use of the authorized product under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). 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), the REGIOCIT, with the required labeling set forth in this section (Section II), are authorized for the uses described above.

III. Conditions of Authorization

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

Baxter Healthcare Corporation

A. Baxter Healthcare Corporation may request changes to the authorized labeling as described in the Scope of Authorization (Section II) of this letter. Such requests will be made in consultation with, and require concurrence of, the Division of Cardiology and Nephrology (DCN)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER).

B. Baxter Healthcare Corporation may request changes to the Scope of Authorization (Section II in this letter) of the product. Such requests will be made in consultation with, and require concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DCN/OCHEN/OND/CDER.

C. Baxter Healthcare Corporation will manufacture REGIOCIT in conformance with Current Good Manufacturing Practices.

D. Baxter Healthcare Corporation will manufacture and test REGIOCIT per the process and methods, including in-process sampling and testing and finished product testing (release and stability) to meet all specifications as referenced in Baxter's EUA request.

E. REGIOCIT will have an 18-month expiry period when stored at room temperature or refrigerated conditions.

F. Baxter Healthcare Corporation will conduct additional endotoxin testing as detailed in Baxter Healthcare Corporation's response, dated July 13, 2020, to FDA's information request, dated July 10, 2020.

G. Baxter Healthcare Corporation 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.

H. Baxter Healthcare Corporation will determine whether an individual facility is qualified, for the purposes of receiving REGIOCIT, in accordance with the process and criteria submitted in Baxter Healthcare Corporation's EUA request. Baxter Healthcare Corporation will maintain documentation on its qualification activities for each individual facility.

I. Baxter Healthcare Corporation will submit information to the Agency within three working days of receipt of any information concerning any batch of REGIOCIT (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the drug 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 drug product, or any failure of one or more batches of the drug product to meet the established specifications.

J. Baxter Healthcare Corporation will report to FDA serious adverse events and all medication errors associated with the use of REGIOCIT of which they become aware during the pandemic, to the extent practicable given emergency circumstances, 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: "use of REGIOCIT was under an 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.

Baxter Healthcare Corporation and Authorized Distributors[7]

K. Baxter Healthcare Corporation will notify FDA of any authorized distributor(s) of the product, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA.

L. Baxter Healthcare Corporation and authorized distributor(s) will make REGIOCIT available with the authorized labeling as described in the Scope of Authorization (Section II) of this letter.

[7] "Authorized Distributor(s)" are identified by the sponsor in EUA requests as an entity allowed to distribute the product.

M. Baxter Healthcare Corporation and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers, the Fact Sheet for Patients, and the REGIOCIT Package Insert for EUA.

N. Through a process of inventory control, Baxter Healthcare Corporation and authorized distributor(s) will maintain records of the healthcare settings to which they distribute REGIOCIT and the number of bags of REGIOCIT distributed.

O. Baxter Healthcare Corporation and authorized distributor(s) will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

P. Baxter Healthcare Corporation and authorized distributor(s) are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

Hospitals and Other Healthcare Facilities to Whom the Authorized REGIOCIT Is Distributed and Healthcare Providers Administering the Authorized REGIOCIT

Q. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized labeling (as described in the Scope of Authorization (Section II) of this letter) is made available to healthcare providers and to patients and caregivers through appropriate means.

R. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGIOCIT (i.e., lot numbers, quantity, receiving site, receipt date), and product storage.

S. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Baxter Healthcare Corporation and/or FDA. Such records will be made available to Baxter Healthcare Corporation, HHS, and FDA for inspection upon request.

T. Healthcare facilities and prescribing health care providers or their designee receiving REGIOCIT will track all medication errors associated with the use of and all serious adverse events that are considered to be potentially attributable to REGIOCIT use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers using one of the following methods:

Option 1: Complete and submit a MedWatch form online (www.fda.gov/medwatch/report.htm)

Option 2: Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (this form can be found via link above).

Call 1-800-FDA-1088 for questions. Submitted reports should state, "use of REGIOCIT was under an EUA" at the beginning of the question "Describe Event" for further

analysis.

Conditions Related to Printed Matter, Advertising and Promotion

U. All descriptive printed matter, including advertising and promotional material, relating to the use of REGIOCIT 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.

V. No descriptive printed matter, including advertising or promotional material, relating to the use of REGIOCIT may represent or suggest that such products are safe or effective.

W. All descriptive printed matter, including advertising and promotional material, relating to the use of REGIOCIT clearly and conspicuously shall state that:

- REGIOCIT is not FDA-approved;
- REGIOCIT has been authorized by FDA for use under an EUA;
- REGIOCIT 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.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of REGIOCIT 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,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

August 23, 2020

Robert P. Kadlec, MD, MTM&H, MS
Assistant Secretary for Preparedness and Response
Office of the Assistant Secretary for Preparedness and Response
Office of the Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Dr. Kadlec:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with 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 (the virus was later named SARS-CoV-2).[1] On March 27, 2020, on the basis of such determination, the Secretary of HHS 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 Act, subject to the terms of any authorization issued under that section.[2]

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication. Based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Convalescent Plasma Expanded Access Protocol (EAP)

[1] U.S. Department of Health and Human Services (HHS). *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] HHS. *Emergency Use Authorization Declaration.* 85 FR 18250 (April 1, 2020). https://www.govinfo.gov/content/pkg/FR-2020-04-01/pdf/2020-06905.pdf.

sponsored by the Mayo Clinic,[3] it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.[4]

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units containing antibodies to SARS-CoV-2 but not qualified as high-titer by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units and are acceptable for use based on an individualized assessment of patient benefit-risk. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials in the coming months. These ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this EUA; providers are encouraged to enroll patients in those trials.

Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of COVID-19 convalescent plasma for treatment of hospitalized patients with 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 COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization (Section II) meet the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause COVID-19, a serious or life-threatening disease or condition, including severe respiratory illness, in humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that COVID-19 convalescent plasma may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of COVID-19 convalescent plasma when used to treat COVID-19 outweigh the known and potential risks of such products; and

[3] A national expanded access protocol (EAP) sponsored by the Mayo Clinic was established in April 2020 and has enrolled ~90,000 subjects as of August 13, 2020. The goal of this uncontrolled, single-arm study is to provide access to COVID-19 convalescent plasma in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease.

[4] Information derived from ongoing clinical trials of COVID-19 convalescent plasma (particularly randomized controlled trials), as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform the risk-benefit assessment for this EUA.

3. There is no adequate, approved, and available alternative to the emergency use of COVID-19 convalescent plasma for the treatment of COVID-19.[5]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The emergency use of the authorized COVID-19 convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.

The Authorized COVID-19 Convalescent Plasma (Product Description):

I am authorizing the use of COVID-19 convalescent plasma, a biologic product to be used for the treatment of hospitalized patients with COVID-19.

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains SARS-CoV-2 antibodies and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. Under this EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30).

Plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma. If a blood establishment is considering using an alternative test in manufacturing in order to qualify high titer COVID-19 convalescent plasma, they should contact the FDA Center for Biologics Evaluation and Research (CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA.

Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the test described above are considered low titer units and must be labeled accordingly. The health care provider may assess whether units with a S/C value of less than 12 are acceptable for use based on an individualized assessment of benefit-risk. FDA will continue to evaluate this recommendation based on additional data that become available.

Health care providers will administer the authorized COVID-19 convalescent plasma with anti-SARS-CoV-2 antibodies according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one COVID-19 convalescent plasma unit (about 200 mL), with administration of additional COVID-19 convalescent plasma units based on the prescribing physician's medical judgment and the patient's clinical response.

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

COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients
- Fact Sheet for Patients and Parents Caregivers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.

Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and are authorized to be made in consultation with, and with concurrence of, the Office of Blood Research and Review (OBRR) Center for Biologics Evaluation and Research (CBER), Counterterrorism Office (CT) Office of the Center Director (OD) CBER, and Office of Counterterrorism and Emerging Threats (OCET) Office of the Chief Scientist (OCS) Office of the Commissioner (OC), as appropriate.

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 COVID-19 convalescent plasma, when used for the treatment of hospitalized patients with COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its 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 COVID-19 convalescent plasma may be effective for the treatment of hospitalized patients with 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 COVID-19 convalescent plasma (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), COVID-19 convalescent plasma is authorized for the treatment of hospitalized patients with COVID-19 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:

ASPR

A. ASPR 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, registered or licensed blood establishments, hospitals, health care providers) involved in distributing or receiving authorized COVID-19 convalescent plasma. ASPR 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).

B. ASPR may request changes to this authorization, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, CT/OD/CBER, and OCET/OCS/OC.

C. ASPR may request changes to the authorized Fact Sheets for COVID-19 convalescent plasma, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, CT/OD/CBER, and OCET/OCS/OC.

D. ASPR will report to FDA serious adverse events and all medication errors associated with the use of the authorized COVID-19 convalescent plasma that are reported to ASPR, or of which ASPR otherwise becomes aware, during the pandemic.

E. ASPR will make available to FDA upon request any records maintained in connection with this EUA.

Registered or Licensed Blood Establishments

F. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.

G. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

H. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).

I. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma

J. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma 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 health care providers and to patients and caregivers, respectively, through appropriate means.

K. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.

L. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.

M. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, 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).

N. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

O. All descriptive printed matter, including advertising and promotional material, relating to the use of the authorized COVID-19 convalescent plasma 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.

P. No descriptive printed matter, including advertising or promotional material, relating to the use of COVID-19 convalescent plasma may represent or suggest that such product is safe or effective.

Q. All descriptive printed matter, including advertising and promotional material, relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:

- COVID-19 convalescent plasma has not been approved or licensed by FDA;
- COVID-19 convalescent plasma has been authorized by FDA under an EUA;
- COVID-19 convalescent plasma is authorized only 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 authorization is terminated or 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,

/s/

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

November 10, 2020

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Advisor Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Phillips:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of bamlanivimab 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.[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]

Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. It is an investigational drug and is not currently approved for any indication.

Based on review of the topline data from the planned interim analysis of Trial J2W-MC-PYAB, also called BLAZE-1 (NCT04427501), an ongoing randomized, double-blind, placebo-controlled, Phase 2 dose finding trial of bamlanivimab monotherapy in outpatients with mild to moderate COVID-19, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when

[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).

used under the conditions described in this authorization, the known and potential benefits of bamlanivimab 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 bamlanivimab 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 bamlanivimab 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 bamlanivimab may be effective in treating mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, 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 bamlanivimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.[3]

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 bamlanivimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab to authorized distributors[4], 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;

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[4] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized bamlanivimab.

- The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and or hospitalization;

- Bamlanivimab is not authorized for use in the following patient populations [5]:

  - 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.

- Bamlanivimab 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 bamlanivimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. Bamlanivimab, injection, 700 mg/20 mL, is a sterile, preservative-free aqueous solution that is to be diluted by using a 250 mL prefilled 0.9% Sodium Chloride Injection infusion solution, withdrawing and discarding 70 mL of 0.9% Sodium Chloride Injection from the infusion bag, and then transferring 20mL of 700mg/20mL bamlanivimab to the 0.9% Sodium Chloride Injection infusion bag. The authorized bamlanivimab includes a vial label and/or carton labeling that is clearly marked for "emergency use authorization".

Bamlanivimab, injection, 700 mg/20 mL, vials should be stored in unopened vials under refrigerated temperature at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Diluted bamlanivimab infusion solution can be stored for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time.

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

Bamlanivimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Lilly's website at www.bamlanivimab.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab
- Fact Sheet for Patients, Parents and Parent Caregivers: Emergency Use Authorization (EUA) of Bamlanivimab for Coronavirus Disease 2019 (COVID-19)

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 bamlanivimab, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its 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 bamlanivimab 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 bamlanivimab (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), bamlanivimab 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, 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:

Eli Lilly and Company (Lilly) and Authorized Distributors

A. Lilly and authorized distributor(s) will ensure that the authorized bamlanivimab 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. Lilly 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. Lilly 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 bamlanivimab. Lilly 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. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bamlanivimab, 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. Lilly will report to FDA serious adverse events and all medication errors associated with the use of the authorized bamlanivimab that are reported to Lilly 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: "use of bamlanivimab was under an 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. Lilly will retain an independent third party (i.e., not affiliated with Lilly) to conduct a review of the batch records and any underlying data and associated discrepancies of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ.

- For all batches manufactured prior to the effective date of this authorization, these batches can be released while review is ongoing.
- For all batches manufactured after the effective date of this authorization, the third party review can be performed concurrent to Lilly's batch release process.

If the independent review finds, prior to release, a discrepancy with significant potential to affect critical quality attributes, the product must not be released unless and until the issue is satisfactorily resolved. Any discrepancies found by the independent review, whether prior to or after release, must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy, including whether market action is required. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

H. Lilly will retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly, Branchburg (excluding bioburden and endotoxin testing). Due to implementation timelines, independent third-party potency testing will commence on February 1, 2021. Until February 1, 2021, the Lilly Indianapolis, IN facility may conduct the equivalent of third-party potency testing. Any discrepancies found by Lilly Indianapolis, IN or the independent laboratory must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

I. Lilly will submit information to the Agency within three working days of receipt of any information concerning any batch of bamlanivimab (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the drug 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 drug product, or any failure of one or more batches of the drug product to meet the established specifications. Lilly 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, Lilly must recall them.

J. Lilly 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.

K. Lilly will manufacture and test bamlanivimab 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 Lilly's EUA request.

L. Lilly will list bamlanivimab with a unique product NDC 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.

M. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized bamlanivimab (i.e., lot numbers, quantity, receiving site, receipt date).

N. Lilly 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 Bamlanivimab Is Distributed and Healthcare Providers Administering the Authorized Bamlanivimab

O. 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 bamlanivimab.

P. Healthcare facilities and healthcare providers receiving bamlanivimab will track serious adverse events that are considered to be potentially attributable to bamlanivimab 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 for questions. Submitted reports should state, "use of bamlanivimab was under an EUA" at the beginning of the question "Describe Event" for further analysis.

Q. 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.

R. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized bamlanivimab (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).

S. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

T. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab 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, as well as advertising or promotional material, relating to the use of bamlanivimab 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 with

positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and or hospitalization.

V. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab clearly and conspicuously shall state that:

- the bamlanivimab has not been approved, but has been authorized for emergency use by FDA, to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and or hospitalization.

- the bamlanivimab is authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and or hospitalization only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the bamlanivimab under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or 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,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

November 19, 2020

Eli Lilly and Company
Attention: Jillian Venci Fuhs, JD, PharmD
Advisor, Global Regulatory Affairs – North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Fuhs:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in certain hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), 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.[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]

Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Baricitinib (Olumiant) is approved by FDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. Baricitinib has not been approved by FDA for the treatment of COVID-19.

[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).

Based on review of the data from the randomized, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone, also called ACTT-2 (NCT04401579), data for baricitinib that FDA reviewed for the FDA-approved indication of rheumatoid arthritis (NDA 207924), and data from populations studied for other indications, including pediatric patients, it is reasonable to believe that baricitinib may be effective, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients 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 baricitinib 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 baricitinib 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 baricitinib, in combination with remdesivir, may be effective in treating suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used in combination with remdesivir to treat COVID-19 in such patients outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.[3, 4]

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

[4] On October 22, 2020, remdesivir was approved to treat COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization. Remdesivir is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-COV-2. Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19. The Adaptive COVID-19 Treatment Trial 2 (ACTT-2) trial provided scientific evidence that the combination of baricitinib plus

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:

- The baricitinib covered by this authorization will be used only by healthcare providers, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized[5] adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO; and

- The use of baricitinib covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

Baricitinib is a Janus kinase (JAK) inhibitor. Baricitinib is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface. Baricitinib tablets are to be taken orally or can be crushed, dispersed in water, and given via a gastrostomy tube. The authorized baricitinib includes commercially available[6] Olumiant (baricitinib) supplied in 30 count bottles as follows:

- OLUMIANT (baricitinib) 1 mg (NDC 0002-4732-30)
- OLUMIANT (baricitinib) 2 mg (NDC 0002-4182-30)

Baricitinib should be stored at 20° to 25°C (68° to 77°F) with excursions permitted to 15° to 30°C (59° to 86°F).

Baricitinib is authorized for emergency use with the FDA-approved package insert and the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Lilly's website at *www.baricitinibemergencyuse.com*:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Baricitinib

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Baricitinib

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remdesivir provided a potential clinically meaningful benefit as compared to remdesivir alone in time to recovery, NIAID Ordinal Scale outcome at Day 15, and progression to ventilation or death at Day 29. Veklury's FDA-approved indication is for a narrower population than the use authorized for baricitinib under this EUA.

[5] Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

[6] For the purposes of this Letter of Authorization, commercially available Olumiant (baricitinib) tablets refers to product in United States distribution under the approved New Drug Application 207924.

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 baricitinib, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its 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 baricitinib 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 baricitinib (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), baricitinib is authorized, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO 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:

Eli Lilly and Company (Lilly) and Authorized Distributors[7]

A. Lilly and authorized distributor(s) will ensure that the authorized baricitinib is distributed and the FDA-approved package insert and 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. Lilly and authorized distributor(s) will ensure that appropriate storage is maintained until the authorized product is delivered to healthcare facilities and/or healthcare providers.

C. Lilly 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 baricitinib. Lilly will provide to all relevant

[7] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized baricitinib.

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. Lilly may request changes to this authorization, including to the authorized Fact Sheets for baricitinib, 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. Lilly will report to FDA serious adverse events and all medication errors associated with the use of the authorized baricitinib that are reported to Lilly 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: "Baricitinib 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. Lilly will submit information to the Agency within three working days of receipt of any information concerning any batch of authorized baricitinib (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the drug 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 drug product, or any failure of one or more batches of the drug product to meet the established specifications. Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

H. Lilly will not implement any changes to the description of the authorized 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. Lilly will manufacture and test authorized baricitinib 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 Lilly's EUA request.

J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized baricitinib (i.e., lot numbers, quantity, receiving site, receipt date).

K. Lilly 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 Baricitinib Is Distributed and Healthcare Providers Administering the Authorized Baricitinib

L. 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 baricitinib for the authorized use.

M. Healthcare facilities and healthcare providers will track serious adverse events that are considered to be potentially attributable to the authorized baricitinib 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 for questions. Submitted reports should state, "Baricitinib treatment under Emergency Use Authorization (EUA)" at the beginning of the question "Describe Event" for further analysis.

N. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the authorized product is administered consistent with the terms of this letter.

O. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized baricitinib (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).

P. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

Q. All descriptive printed matter, advertising, and promotional material relating to the use of the baricitinib 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.

R. No descriptive printed matter, advertising, or promotional material relating to the use of baricitinib under this authorization may represent or suggest that such products are safe or effective when used, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

S. All descriptive printed matter, advertising, and promotional material relating to the use of the baricitinib under this authorization clearly and conspicuously shall state that:

- the baricitinib has not been approved, but has been authorized for emergency use by FDA, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

- the baricitinib is authorized, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the baricitinib under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or 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,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

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.[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]

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

[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).

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.[3]

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)[4], who will distribute to healthcare facilities or healthcare providers as

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

  - 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.

[5] 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:

- 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), 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 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,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Dated: February 16, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021–03429 Filed 2–18–21; 8:45 am]

BILLING CODE 4164–01–C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended, notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The contract proposals and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the contract proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Allergy and Infectious Diseases Special Emphasis Panel; RFP–NIH–NIAID–DAIT–75N93020R00018: Transplantation Statistical and Clinical Coordinating Center (T–SCCC).

Date: March 18, 2021.

Time: 10:00 a.m. to 5:00 p.m.

Agenda: To review and evaluate contract proposals.

Place: National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 3G53, Rockville, MD 20892 (Virtual Meeting).

Contact Person: Konrad Krzewski, Ph.D., Scientific Review Officer, Scientific Review Program, Division of Extramural Activities, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 3G53, Rockville, MD 20852, 240–747–7526, *konrad.krzewski@nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Dated: February 12, 2021.

Tyeshia M. Roberson,

Program Analyst, Office of Federal Advisory Committee Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Notice of Closed Meeting

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Name of Committee: Microbiology, Infectious Diseases and AIDS Initial Review Group; Microbiology and Infectious Diseases B Subcommittee MID–B Review Committee 03/2021.

Date: March 15–17, 2021.

Time: 11:00 a.m. to 6:00 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 3F30, Rockville, MD 20892 (Virtual Meeting).

Contact Person: Ellen S. Buczko, Ph.D., Scientific Review Officer, Scientific Review Program, Division of Extramural Activities, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 3F30, Rockville, MD 20852, 301–451–2676, *ebuczko1@niaid.nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)