

October 27, 2022

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

RE: Emergency Use Authorization 111

Dear Ms. Phillips:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients who are at high-risk for progression to severe COVID-19, including hospitalization or death, 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 coronavirus disease 2019 (COVID-19).¹ On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.²

On February 11, 2022, the FDA issued an EUA for the emergency use of bebtelovimab 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) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

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).

Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the Letter of Authorization (LOA) on August 5, 2022.³

On October 27, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 5, 2022 letter in its entirety, to incorporate clarifying revisions to Condition W of this letter. Condition V was also revised to require that all printed matter, advertising and promotional materials relating to the use of bebtelovimab under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Based on the review of the data from the BLAZE-4 clinical trial (NCT04634409), a Phase 1/2 randomized, single-dose clinical trial studying bebtelovimab for the treatment of non-hospitalized patients with mild-to-moderate COVID-19, as well as available pharmacokinetic data and nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab 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) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab 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 bebtelovimab 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) who are at high-risk for progression to severe COVID-19, including hospitalization or death, 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 bebtelovimab for treatment of mild-to-moderate 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 bebtelovimab 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) who

³ In its August 5, 2022 revision, FDA revised the LOA with revisions to the scope of authorization no longer requiring directed distribution of bebtelovimab by the United States Government.

are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative⁴ to the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric (12 years of age and older weighing at least 40 kg) patients as further described in the Scope of Authorization (section II).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:

- Bebtelovimab may only be 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-risk⁶ for progression to severe COVID, including hospitalization or death, and
 - For whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.
- Bebtelovimab is **not** authorized for use in the following patient populations⁷:
 - Adults or pediatric patients who are hospitalized due to COVID-19, or
 - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19-related comorbidity;
- Bebtelovimab is **not** authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

⁴ Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults and pediatric patients within the scope of this authorization, FDA does not consider it to be an adequate alternative for certain patients for whom it may not be feasible or practical (e.g., it requires a 3-day treatment duration).

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

⁶ For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>.

⁷ Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.⁸

- Bebtelovimab 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 bebtelovimab covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

Bebtelovimab injection (NDC 0002-7589-01) is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial. Each carton contains a single vial of bebtelovimab, which is labeled “For Use Under Emergency Use Authorization (EUA)”.

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

Bebtelovimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers, respectively, through Lilly’s website www.LillyAntibody.com/bebtelovimab (referred to as the “authorized labeling”):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for bebtelovimab
- Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of bebtelovimab 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 bebtelovimab, 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 bebtelovimab 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.

⁸ FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>. FDA’s determination and any updates will be available at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that bebtelovimab (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 bebtelovimab under this 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), bebtelovimab is authorized for the treatment of COVID-19 as described in this 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:

Lilly and Authorized Distributors⁹

- A. Lilly and authorized distributor(s) will ensure that the authorized bebtelovimab is distributed 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 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 bebtelovimab. 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).
- C. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bebtelovimab. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.¹⁰

⁹ “Authorized Distributor(s)” are identified by Lilly as an entity or entities allowed to distribute the authorized bebtelovimab.

¹⁰ The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and

D. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of bebtelovimab as described in this Letter of Authorization and authorized labeling, without FDA’s review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for bebtelovimab are prohibited. If the Agency notifies Lilly that any instructional and educational materials are inconsistent with the authorized labeling, Lilly must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

E. Lilly will report to FDA all serious adverse events and medication errors potentially related to bebtelovimab use 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 must state: “Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA).” For reports submitted under Option 1, include this language at the beginning of the question “Describe Event” for further analysis. For reports submitted under Option 2, include this language at the beginning of the “Case Narrative” field.

F. All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

G. Lilly will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of bebtelovimab that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

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.

If not included in its initial notification, Lilly must submit information confirming that Lilly has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Lilly must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- H. Lilly will manufacture bebtelovimab to meet all quality standards and per the manufacturing process and control strategy as detailed in Lilly's EUA request. 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 as described under condition D.
- I. Lilly will list bebtelovimab with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.
- J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of bebtelovimab (i.e., lot numbers, quantity, receiving site, receipt date).
- K. Lilly will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Lilly's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Lilly will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.
- L. FDA may require Lilly to assess the activity of the authorized bebtelovimab against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Lilly will perform the required assessment in a manner and timeframe agreed upon by Lilly and the Agency. Lilly will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Lilly will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

- M. Lilly shall provide samples as requested of the authorized bebtelovimab to the HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized bebtelovimab may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.
- N. Lilly must provide the following information to the Agency:
1. Lilly will submit a study report to FDA characterizing the development of SARS-CoV-2 resistance to bebtelovimab in cell culture passage experiments no later than 30 days of the completion of these experiments.
 2. Lilly will submit to FDA all sequencing data assessing bebtelovimab, including sequencing of any participant samples from the full analysis population from PYAH arms 9-14 that have not yet been completed no later than March 31, 2022.
 3. Lilly will submit a proposed clinical trial protocol to further evaluate bebtelovimab for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients no later than March 1, 2022.
- O. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom Bebtelovimab Is Distributed and Healthcare Providers Administering bebtelovimab

- P. 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 bebtelovimab as described in the Scope of Authorization (Section II) under this EUA.
- Q. Healthcare facilities and healthcare providers receiving bebtelovimab will track all serious adverse events and medication errors that are considered to be potentially related to bebtelovimab use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call [1-800-FDA-1088](tel:1-800-FDA-1088) for questions. Submitted reports must state, “Bebtelovimab use for COVID-19 under Emergency Use Authorization” at the beginning of the question “Describe Event” for further analysis.

- R. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.
- S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of bebtelovimab for the use authorized in this letter (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).
- T. 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.
- U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

- V. All descriptive printed matter, advertising, and promotional materials relating to the use of bebtelovimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to “approved labeling”, “permitted labeling” or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of bebtelovimab under this authorization. In addition, such materials shall:
 - Be tailored to the intended audience.
 - Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
 - Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
 - Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
 - Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.
- W. Lilly may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of bebtelovimab that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Lilly may not imply that bebtelovimab is FDA-approved for its authorized use by making statements such as “bebtelovimab is safe and effective for the treatment of COVID-19.”

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

- Bebtelovimab has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate; and
- The emergency use of bebtelovimab 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.

If the Agency notifies Lilly that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions V through X of this EUA, Lilly must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

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/--

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration