

December 20, 2021

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:

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

On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of baricitinib (Olmiant), 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). 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 (Olmiant tablets 1 mg and 2 mg) 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.

FDA reissued the Letter of Authorization on July 28, 2021, to no longer require that baricitinib be used in combination with remdesivir.³

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

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

³ While the Letter of Authorization authorized the use of baricitinib alone for the uses detailed in the Scope of Authorization (Section II), the Agency notes that the COV-BARRIER trial supporting this authorization did not

On December 20, 2021, again 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 July 28, 2021 letter in its entirety to include the authorized use of the baricitinib 4 mg tablets and to reference authorized storage and handling within the authorized Fact Sheet for Healthcare Providers.

Based on the review of data from the clinical trial ACTT-2 (NCT04401579), a 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; data from COV-BARRIER (NCT04421027), a randomized, double-blind, placebo-controlled clinical trial conducted by the NIAID comparing treatment with baricitinib to placebo in hospitalized adults with confirmed SARS-CoV-2 infection; data for baricitinib that FDA has 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 for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or 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 may be effective in treating COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib to treat COVID-19 in such patients outweigh the known and potential risks of such product; and

raise questions about the safety or efficacy of baricitinib used in combination with remdesivir for the treatment of patients hospitalized due to COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. As such, the use of baricitinib in combination with remdesivir is not contraindicated under the terms and conditions of this authorization.

3. There is no adequate, approved, and available alternative to the emergency use of baricitinib for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.^{4, 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:

- The baricitinib covered by this authorization will be used only by healthcare providers to treat COVID-19 in hospitalized⁶ adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or 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 is supplied in 30 count bottles as follows:

- commercially available⁷ OLUMIANT (baricitinib) tablet 1 mg (NDC 0002-4732-30)
- commercially available⁷ OLUMIANT (baricitinib) tablet 2 mg (NDC 0002-4182-30)
- baricitinib tablet 4 mg (NDC 0002-6885-30)

The authorized baricitinib tablet 4 mg includes container labeling that is marked “For use under Emergency Use Authorization (EUA)”. The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

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

⁵ On October 22, 2020, Veklury (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. Veklury 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. This is distinct from Veklury, which acts as an antiviral agent. We also note that Veklury’s FDA-approved indication is for a narrower population than the use authorized for baricitinib under this EUA.

⁶ 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.

⁷ 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.

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 (referred to as the “authorized labeling”):

- 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

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 to treat COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or 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 Distributors⁸

- 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) as

⁸“Authorized Distributor(s)” are identified by Lilly as an entity or entities allowed to distribute authorized baricitinib.

described in Section II of this Letter of Authorization will be made available to healthcare facilities and/or healthcare providers.

- 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 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. Any request for changes to this EUA must be submitted to the Division of Rheumatology and Transplant Medicine/Office of Immunology and Inflammation/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.⁹
- E. 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 baricitinib 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 baricitinib are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for baricitinib, the Agency will require Lilly to cease distribution of such instructional and educational materials.
- F. 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.

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

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 use for COVID-19 under Emergency Use Authorization (EUA).” For reports submitted under Option 1, include this language at the beginning of the question “Describe Event” for further analysis. For reports submitted under Option 2, include this language at the beginning of the “Case Narrative” field.

- G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.
- H. Lilly will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this emergency use authorization for baricitinib 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 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 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.

- I. Lilly will manufacture baricitinib 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.

- 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.
- L. Lilly will list baricitinib 4 mg tablets 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.

Healthcare Facilities to Whom the Authorized Baricitinib Is Distributed and Healthcare Providers Administering the Authorized Baricitinib

- 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 baricitinib for the authorized use.
- N. Healthcare facilities and healthcare providers will track serious adverse events and medication errors 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](tel:1-800-FDA-1088) for questions. Submitted reports should state, “Baricitinib use for COVID-19 under Emergency Use Authorization (EUA)” at the beginning of the question “Describe Event” for further analysis. A copy of the completed FDA Form 3500 should also be provided to Lilly per the instructions in the authorized labeling.
- O. 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 and the authorized labeling.
- P. 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).
- Q. 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

- R. 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 meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. Reference to “approved labeling”, “permitted labeling” or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of baricitinib 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 at the time of initial dissemination or first use.

If the Agency notifies Lilly that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions Q-S 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).

- S. 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 for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.
- T. 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 for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.
 - The emergency use of baricitinib is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

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

Sincerely,

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Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration