

# Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules

## Center for Drug Evaluation and Research Review Memorandum

### Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000108
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. 1 Merck Drive PO Box 100 Whitehouse Station, NJ 08889-0100 908-423-1000  POC: Sushma Kumar, PhD, PMP Senior Director, Global Regulatory Affairs and Clinical Safety Merck Sharp & Dohme Corp.  (b) (6)
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	Lagevrio
Established Name/Other names used during development	Molnupiravir (MK-4482; MOV; EIDD-2801)
Dosage Forms/Strengths	Oral capsule, 200 mg
Therapeutic Class	SARS-CoV-2 antiviral
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults with a current diagnosis of mild-to-moderate COVID-19, 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.

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

## Rationale for Revisions to EUA Letter of Authorization (LOA) and Fact Sheets

The LOA for the Lagevrio EUA and authorized Fact Sheets are being revised at this time for the following reasons:

### 1. To revise the Scope of Authorization in the LOA to remove the requirement on USG-directed distribution of Lagevrio

Since initial issuance of the EUA for Lagevrio, the Scope of Authorization in the LOA has included the following language:

Distribution of the authorized LAGEVRIO will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Merck will supply LAGEVRIO to authorized distributor(s), 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.

This condition on the authorization helped ensure, among other things, equitable distribution of the USG-procured inventory of Lagevrio. Beginning in October, 2023, the USG will transition from a USG-directed distribution framework for Lagevrio to a distribution framework controlled by Merck.<sup>1</sup> As part of this transition, Lagevrio will become available for commercial purchase. FDA is revising the LOA for the Lagevrio EUA to facilitate this transition. The USG-procured inventory of Lagevrio is labeled with a unique NDC and is distinct from the unique NDC that is on the labeling for Lagevrio that will be available for commercial purchase.

### 2. To revise Condition K and Conditions Related to Printed Matter, Advertising and Promotion in the LOA

#### Revision to Condition K

FDA is revising condition K in the LOA for the Lagevrio EUA to remove examples in the parenthetical describing the types of inventory control processes and distribution records to be captured. As revised, condition K will still require that Merck maintain records regarding the distribution of the product as a part of their inventory control processes which remain applicable. The deletion of the parenthetical will allow for flexibility based on current business practices. Additionally, Merck notes that their direct distributors inventory control processes, including records maintenance, will remain compliant with relevant federal, state and local laws and regulations, which includes information and requirements including and beyond what is contained in the parenthetical language.

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<sup>1</sup> See statement from the United States Administration for Strategic Preparedness and Response, dated September 29, 2023 at: <https://aspr.hhs.gov/COVID-19/Therapeutics/updates/Pages/important-update-Sept2023.aspx>

## Revision to LOA Conditions Related to Printed Matter, Advertising and Promotion

FDA is revising the Conditions Related to Printed Matter, Advertising and Promotion of the Lagevrio LOA to clarify that reminder advertisements and reminder labeling intended only to provide price information to consumers are permissible, so long as the conditions in 21 CFR 200.200 are met.

Given the transition from USG-controlled distribution of Lagevrio to Merck-controlled commercial distribution of Lagevrio under the EUA, FDA believes it is important to remove this potential barrier to consumers having up-to-date pricing information for the commercialized product. The LOA for the Lagevrio EUA continues to state, in part, that all descriptive printed matter, advertising, and promotional materials relating to the use of Lagevrio under the authorization shall meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. Any reminder advertising (or reminder labeling) for Lagevrio related to pricing information must meet all of the required conditions described in 21 CFR 200.200. Per the LOA, Merck must submit promotional materials to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

### **3. To revise the LOA and authorized Fact Sheets to remove the requirement for “a current diagnosis of” mild-to-moderate COVID-19.**

Language revised for consistency with other products that are either FDA-approved or authorized for emergency use under EUA for the same use authorized for Lagevrio.

### **4. To add information on PAXLOVID as an Approved Available Alternative**

On May 25, 2023, the FDA approved the oral antiviral Paxlovid (nirmatrelvir tablets and ritonavir) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Accordingly, Paxlovid is an approved alternative to Lagevrio. The Fact Sheets are being revised to reflect the approval of Paxlovid and to explain how Paxlovid is not considered an adequate alternative to Lagevrio.<sup>2</sup> In addition, the factsheets are being revised to remove references to other therapeutics currently *authorized* for the same use as Lagevrio, as there are not currently any products authorized for this use.

### **5. Update the *Justification for Emergency Use of Drugs During the COVID-19 Pandemic* section**

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<sup>2</sup> See 564(c)(3) of the Federal Food, Drug and Cosmetic Act.

This section of the Fact Sheet for Healthcare Providers has been revised to include clarifying edits justifying the emergency use of drug during the COVID-19 pandemic.

**6. To revise the LOA and authorized Fact Sheets to remove section 6.5 *Other Reporting Requirements***

Merck proposes to remove the requirement for healthcare facilities and providers to report therapeutics information and utilization data given that the U.S. government will no longer be distributing molnupiravir. FDA agrees with this revision.

## **Summary of Fact Sheet Revisions**

All substantive changes to the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients and Caregivers are shown below. Please note that edits were also made to the Frequently Asked Questions Document for consistency. All current documents pertaining to this EUA can be found here: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>. These changes were made for consistency with updated information regarding approval of Paxlovid and the public health emergency.

## **FACT SHEET FOR HEALTHCARE PROVIDERS**

*Sections with significant changes are shown below with edits denoted in red and strikethrough fonts.*

### **MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION**

Item 3.ii in the Mandatory Requirements Box has been updated as follows:

- ii. Other therapeutics are currently approved ~~or authorized~~ for the same use as LAGEVRIO [see Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use].

### **1 EMERGENCY USE AUTHORIZATION**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product LAGEVRIO™ for treatment of adults with ~~a current diagnosis of~~ mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

### Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has ~~declared that~~:

- Determined that there is a public health emergency, or significant potential for a public health emergency, related to COVID-19<sup>3</sup>. ~~A public health emergency related to COVID-19 has existed since January 27, 2020.~~
- Declared that ~~c~~Circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19<sup>4</sup>. ~~during the COVID-19 pandemic (March 27, 2020 declaration).~~

## APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (at least 28 days old and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an approved alternative to LAGEVRIO for the treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to LAGEVRIO for this authorized use because it may not be feasible or clinically appropriate for certain patients (e.g., it requires a 3-day intravenous treatment duration).

Paxlovid (nirmatrelvir tablets; ritonavir tablets co-packaged for oral use) is FDA-approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid is administered orally for a total treatment duration of 5 days. Although Paxlovid is an approved alternative to LAGEVRIO for the treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Paxlovid to be an adequate alternative to LAGEVRIO for this authorized use because it may not be clinically appropriate for patients on medications that are primarily metabolized by CYP3A and/or that are strong CYP3A inducers.

~~Other therapeutics are currently authorized for the same use as LAGEVRIO.~~ For additional information on all products authorized for treatment or prevention of COVID-

<sup>3</sup> See 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; <https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency>. See also U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); <https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration>.

<sup>4</sup> See 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); <https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration>. See also Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

19, please see <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> .

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **6.5 Other Reporting Requirements**

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

## **FACT SHEET FOR PATIENTS AND CAREGIVERS**

*Sections with significant changes are shown below with edits denoted in red and strikethrough fonts.*

You are being given this fact sheet because your healthcare provider believes it is necessary to provide you with LAGEVRIO for the treatment of adults with ~~a current diagnosis of~~ mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom other COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate.

### **What other treatment choices are there?**

Veklury (remdesivir) is FDA-approved as an intravenous (IV) infusion for the treatment of mild-to-moderate COVID-19 in certain adults and children. ~~Paxlovid (nirmatrelvir/ritonavir) is FDA-approved as tablets for the treatment of mild-to-moderate COVID-19 in certain adults.~~ Talk with your doctor to see if Veklury ~~or Paxlovid are~~is appropriate for you.

- Visit [www.molnupiravir.com](http://www.molnupiravir.com)

### **What Is an Emergency Use Authorization (EUA)?**

The United States FDA has made LAGEVRIO available under an emergency access mechanism called an Emergency Use Authorization (EUA) The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify emergency use of drugs and biological products during the COVID-19 pandemic.

LAGEVRIO ~~is authorized for emergency use~~ for the treatment of adults with ~~a current diagnosis of~~ mild-to-moderate COVID-19 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.

~~LAGEVRIO as a treatment for COVID-19, has not undergone the same type of review as an FDA-approved product. The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety,~~

performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

### **Regulatory Conclusion and Associated Actions:**

The Division of Antivirals and Office of Infectious Diseases recommends revision to EUA 108 as outlined above in order to protect the public health and to provide healthcare providers and patients with the most current information regarding LAGEVRIO.

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