Promoting the Quality of Medicines Plus (PQM+)

Scientific and technical information package for COVID-19 antivirals prescribed to prevent serious disease and death in high-risk populations infected with COVID-19

Nirmatrelvir tablets co-packaged with Ritonavir tablet; Molnupiravir capsule

August 2023

Package 3C

USAID FROM THE AMERICAN PEOPLE

usp

Contact Information

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

Suggested Citation

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Contents

Acknowledgements

European Medicines Agency (EMA) authored documents are cited in their original form as published by EMA (either as a PDF or online publication).

U.S. Food and Drug Administration (FDA) authored documents are cited in their original form as published by U.S. FDA. Advisory committee briefing documents provided to the U.S. FDA by Pfizer and Merck Sharp & Dohme LLC are for public release and were published on the U.S. FDA website.

U.S. National Institutes of Health (NIH) documents were authored by the COVID-19 Treatment Guidelines Panel. Specifically, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2023. The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (https://www.covid19treatmentguidelines.nih.gov/).

World Health Organization (WHO)-authored documents are cited in their original form as published by WHO (either as a PDF or online publication). Individual titles, place of publication, and year are contained in each original document except the one listed below. All documents were issued under License: CC BY-NC-SA 3.0 IGO

PQM+ would like to thank our implementing partner programs, Meeting Targets and Maintaining Epidemic Control (EpiC) and Reaching Impact, Saturation, and Epidemic Control (RISE), for their collaboration and support throughout the test-to-treat (T2T) program. We would also like to thank our collaborators from the national medicines regulatory authorities (NMRA) in each of the Test to Treat countries:

Directorate General of Drug Administration, Bangladesh
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Direccion Nacional de Medicamentos, El Salvador
Food and Drugs Authority Ghana
Ministry of Health, Lesotho
Pharmacy and Medicines Regulatory Authority, Malawi
Autoridade Nacional Reguladora de Medicamentos, Mozambique
Rwanda Food and Drugs Authority
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Acronyms

API	active pharmaceutical ingredients
EMA	European Medicines Agency
EUA	emergency use authorization
EUAL	emergency use assessment and listing
EUL	emergency use listing
FDA	U.S. Food and Drug Administration
NIH	U.S. National Institutes for Health
PHEIC	public health emergency of international concern
PQM+	Promoting the Quality of Medicines Plus
T2T	test-to-treat
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Package 3C. Tier C Document information (click each entry to link to document)

#	DOCUMENT TITLE	SOURCE
3C.1	EMA Refusal of the marketing authorisation for Lagevrio (molnupiravir)	EMA
3C.2	EMA Question and Answers on Withdrawal of Application for the Marketing Authorization of Lagevrio (molnupiravir)	EMA
3C.3	Letter for the Withdrawal of Marketing Authorization Application for Lagevrio, molnupiravir, 200 mg hard capsules, EMEA/H/C/005789	Merck
3C.4	U.S. FDA EUA Authorization letter – Lagevrio (February 1, 2023)	U.S. FDA
3C.5	U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19	U.S. FDA
3C.6	U.S. FDA Molnupiravir checklist tool for prescribers	U.S. FDA
3C.7	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (March 23, 2022)	U.S. FDA
3C.8	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)	U.S. FDA

RETURN TO PACKAGE TABLE

Document 3C.1

EMA Refusal of the marketing authorisation for Lagevrio (molnupiravir)

Document URL

https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-lagevrio-molnupiravir_en.pdf

Reference website URL

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions-any-scientific-matter-human-medicines#use-of-lagevrio-(also-known-as-molnupiravir-or-mk-4482)-for-treating-covid-19-section

License

Not applicable

EMA/82948/2023 Rev.1
EMEA/H/C/005789

Update as of 13 March 2023:

The applicant for Lagevrio has requested a re-examination of EMA's February 2023 opinion. Upon receipt of the grounds of the request, the Agency will re-examine its recommendation and issue a final recommendation.

24 February 2023

Refusal of the marketing authorisation for Lagevrio (molnupiravir)

The European Medicines Agency has recommended the refusal of the marketing authorisation for Lagevrio, a medicine intended for the treatment of COVID-19 in adults.

The Agency issued its opinion on 23 February 2023. The company that applied for authorisation, Merck Sharp & Dohme B.V., may ask for re-examination of the opinion within 15 days of receiving the opinion.

What is Lagevrio and what was it intended to be used for?

Lagevrio was developed as a medicine for the treatment of adults with COVID-19 who did not require supplemental oxygen and who were at increased risk of developing severe COVID-19.

Lagevrio contains the active substance molnupiravir and was to be available as capsules to be taken by mouth.

How does Lagevrio work?

The active substance in Lagevrio, molnupiravir, is an antiviral medicine that reduces the ability of SARS-CoV-2 (the virus that causes COVID-19) to multiply in the body. It does this by increasing the number of alterations (mutations) in the virus' genetic material (known as RNA) in a way that impairs the ability of SARS-CoV-2 to multiply.

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RETURN TO PACKAGE TABLE

What did the company present to support its application?

The company submitted the results of one main study investigating Lagevrio in over 1,400 non-hospitalised, unvaccinated adults with at least one underlying condition putting them at risk of severe COVID-19. This study compared Lagevrio with placebo (a dummy treatment). The company also provided supportive data from other studies and real-world data on the use of molnupiravir in clinical practice.

What were the main reasons for refusing the marketing authorisation?

Having evaluated the data provided by the company, EMA's human medicines committee (CHMP) concluded that the clinical benefit of Lagevrio in the treatment of adults with COVID-19 who are not receiving supplemental oxygen and who are at increased risk of developing severe COVID-19 could not be demonstrated.

Based on the totality of data, it was not possible to conclude that Lagevrio can reduce the risk of hospitalisation or death or shorten the duration of illness or time to recovery in adults at risk of severe disease. Furthermore, it was not possible to identify a specific group of patients in whom a clinically relevant benefit of Lagevrio could be demonstrated.

Therefore, the Agency's opinion was that the balance of benefits and risks of Lagevrio in the treatment of COVID-19 could not be established. Hence, the Agency recommended refusing marketing authorisation.

Does this refusal affect patients in clinical trials?

The company informed the Agency that there are no consequences for patients in clinical trials with molnupiravir. If you are in a clinical trial and need more information about your treatment, speak with your clinical trial doctor.

RETURN TO PACKAGE TABLE

Document 3C.2

EMA Question and Answers on Withdrawal of Application for the Marketing Authorization of Lagevrio (molnupiravir)

Document URL

https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-application-marketing-authorisation-lagevrio-molnupiravir_en-0.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/lagevrio#:~:text=Overview-,Overview,intended%20to%20be%20used%20for%3F

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Not applicable

RETURN TO PACKAGE TABLE

27 June 2023
EMA/296884/2023
EMEA/H/C/005789

Withdrawal of application for the marketing authorisation of Lagevrio (molnupiravir)

On 21 June 2023, Merck Sharp & Dohme B.V. withdrew its application for a marketing authorisation of Lagevrio for the treatment of COVID-19 in adults.

What is Lagevrio and what was it intended to be used for?

Lagevrio was developed as a medicine for the treatment of adults with COVID-19 who did not require supplemental oxygen and who were at increased risk of developing severe COVID-19.

Lagevrio contains the active substance molnupiravir and was to be available as capsules to be taken by mouth.

How does Lagevrio work?

The active substance in Lagevrio, molnupiravir, is an antiviral medicine that reduces the ability of SARS-CoV-2 (the virus that causes COVID-19) to multiply in the body. It does this by increasing the number of alterations (mutations) in the virus' genetic material (known as RNA) in a way that impairs the ability of SARS-CoV-2 to multiply.

What did the company present to support its application?

The company submitted the results of one main study investigating Lagevrio in over 1,400 non-hospitalised, unvaccinated adults with at least one underlying condition putting them at risk of severe COVID-19. This study compared Lagevrio with placebo (a dummy treatment). The company also provided supportive data from other studies and real-world data on the use of molnupiravir in clinical practice.

How far into the evaluation was the application when it was withdrawn?

The evaluation had completed and the European Medicines Agency had recommended refusing marketing authorisation. The company had requested a re-examination of the Agency's recommendation, but it withdrew the application before this re-examination had finished.

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RETURN TO PACKAGE TABLE

What did the Agency recommend at that time?

At the time of the withdrawal, the Agency's human medicines committee (CHMP) had recommended refusing marketing authorisation for Lagevrio for the treatment of adults with COVID-19.

Having evaluated the data provided by the company, the CHMP had concluded that the clinical benefit of Lagevrio in the treatment of adults with COVID-19 who are not receiving supplemental oxygen and who are at increased risk of developing severe COVID-19 had not been demonstrated.

Based on the totality of data, it was not possible to conclude that Lagevrio can reduce the risk of hospitalisation or death or shorten the duration of illness or time to recovery in adults at risk of severe disease. Furthermore, it was not possible to identify a specific group of patients in whom a clinically relevant benefit of Lagevrio had been demonstrated.

Therefore, the Agency's opinion was that the balance of benefits and risks of Lagevrio in the treatment of COVID-19 could not be established. Hence, the Agency had recommended refusing marketing authorisation.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of the application, the company stated that its decision was based on the CHMP's view that the data provided do not allow the committee to conclude on a positive benefit-risk balance for Lagevrio.

Does this withdrawal affect patients in clinical trials?

The company informed the Agency that there are no consequences for patients in clinical trials using molnupiravir. If you are in a clinical trial and need more information about your treatment, speak with your clinical trial doctor.

RETURN TO PACKAGE TABLE

Document 3C.3

Letter for the Withdrawal of Marketing Authorization Application for Lagevrio, molnupiravir, 200 mg hard capsules, EMEA/H/C/005789

Document URL

https://www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-lagevrio_en.pdf

Reference website URL

https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/lagevrio#:~:text=Overview-,Overview,intended%20to%20be%20used%20for%3F

License

Not applicable

Merck Sharp & Dohme (Europe), Inc.
Siège d'exploitation: Boulevard du Souverain 1170 Bruxelles
Exploitatiezetel: Vorstlaan 25 1170 Brussel
c/o : PO Box 20, 5340 BH Oss, The Netherlands

[redacted]

MSD

To: Chair of the CHMP, Dr. Harald Enzmann
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam (The Netherlands)

21 June 2023

Subject: Withdrawal of Marketing Authorization Application for LAGEVRIO, molnupiravir, 200 mg hard capsules, EMEA/H/C/005789

Dear Dr Enzmann,

I would like to inform you that, at this point of time, Merck Sharp & Dohme B.V. has taken the decision to withdraw the application for Marketing Authorization of LAGEVRIO (molnupiravir), 200 mg hard capsules, which was intended to be used for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

This withdrawal is based on the following reason: MSD has taken this decision based on the CHMP's view that the data provided do not allow the committee to conclude on a positive benefit-risk balance for LAGEVRIO at this time.

MSD respectfully disagrees with the CHMP's assessment, and considers that the totality of the scientific evidence, including the positive results from the Phase 3 placebo-controlled trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, supports a positive benefit-risk assessment for LAGEVRIO for the treatment of adults with COVID-19.

We would like to take this opportunity to thank the (Co-)Rapporteurs, CHMP and EMA for their time reviewing this application.

We reserve the right to make further submissions at a future date in this or other therapeutic indication(s).

I agree for this letter to be published on the EMA website in a redacted manner.

Yours sincerely,

[redacted]

[redacted]

[redacted]

RETURN TO PACKAGE TABLE

RETURN TO PACKAGE TABLE

Document 3C.4

U.S. FDA EUA Authorization letter – Lagevrio (February 1, 2023)

Document URL

https://www.fda.gov/media/155053/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

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RETURN TO PACKAGE TABLE

February 1, 2023

Merck Sharp & Dohme LLC
Attention: Sushma Kumar, PhD, PMP
Senior Director, Global Regulatory Affairs and Clinical Safety
1 Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100

RE: Emergency Use Authorization 108

Dear Dr. Kumar:

This letter is in response to Merck Sharp & Dohme Corp.'s (Merck) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of LAGEVRIO (molnupiravir)[1] for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults 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).[2] 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.[3]

On December 23, 2021 the Food and Drug Administration (FDA) issued an EUA for emergency use of LAGEVRIO as treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

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[1] The December 23, 2021, and February 11, 2022 Letters of Authorization (LOA) referred to the authorized drug as "molnupiravir,"; however, Merck subsequently requested, and FDA concurred, that the Fact Sheets be revised to add references to molnupiravir's trade name, "LAGEVRIO." "LAGEVRIO" is used in this March 23, 2022 reissued letter.

[2] 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.

[3] 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).

RETURN TO PACKAGE TABLE

LAGEVRIO capsules contain molnupiravir; a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. LAGEVRIO is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the LOA on February 11, 2022[4], March 23, 2022[5], and August 5, 2022[6], and October 27, 2022.[7]

On February 1, 2023, 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 October 27, 2022 letter in its entirety, to revise the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization now requires, in addition to other requirements, that adults have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes have also been made to the authorized Fact Sheets. Conditions P and U in this letter and the Fact Sheets have been revised to include updated information on the collection of pregnancy exposure and outcomes data through a pregnancy registry. The Fact Sheets have also been revised to include information on administering LAGEVRIO via nasogastric and orogastric tubes. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include additional carcinogenicity and virology information.

Based on the review of the data from the MOVe-OUT clinical trial (NCT04575597), a Phase III randomized, double-blind, placebo-controlled clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that LAGEVRIO may be effective 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, 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 LAGEVRIO outweigh the known and potential risks of such product.

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[4] In its February 11, 2022 revision, FDA revised the scope of this LOA to account for the FDA approval of Veklury (remdesivir) for the treatment of 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, 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. The letter of authorization was also revised to include a new condition regarding registration and listing. The authorized Fact Sheets were also revised to reflect the revision to the scope of authorization for LAGEVRIO as described above and include information on post-authorization reports of hypersensitivity reactions and rashes.

[5] In its March 23, 2022 revision, FDA revised this LOA to add references to molnupiravir's trade name, "LAGEVRIO". Corresponding revisions were also made to the authorized Fact Sheets. The Fact Sheet for Healthcare Providers was also revised to include updated antiviral activity and resistance information.

[6] In its August 5, 2022 revision, FDA revised this LOA to update certain post-authorization requirements as detailed in Condition O of this letter. The Fact Sheet for Healthcare Providers was also revised to include additional virology information and to identify Veklury (remdesivir) as an approved alternative to Lagevrio.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition BB of this letter. Condition AA was also revised to require that all printed matter, advertising and promotional materials relating to the use of LAGEVRIO under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

RETURN TO PACKAGE TABLE

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 LAGEVRIO 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, 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 LAGEVRIO 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 LAGEVRIO may be effective 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, 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 LAGEVRIO outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative[8] to the emergency use of LAGEVRIO for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 as further described in the Scope of Authorization (section II).[9]

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 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)[10], 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;

- LAGEVRIO may only be used for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19:

[8] Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults 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).
[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[10] "Authorized Distributor(s)" are identified by Merck as an entity or entities allowed to distribute authorized molnupiravir.

RETURN TO PACKAGE TABLE

- Who are at high risk[11] 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.

Limitations on Authorized Use

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age.
- LAGEVRIO is not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19.[12] Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.

- LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state[13] law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

- The use of LAGEVRIO covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

The authorized LAGEVRIO is supplied as a bottle (NDC-0006-5055-06, NDC-0006-5055-07, NDC-0006-5055-09) containing a sufficient quantity of LAGEVRIO 200 mg capsules to complete a full treatment course (i.e., 40 capsules). LAGEVRIO is manufactured as a Swedish Orange, opaque capsule containing the Merck corporate logo and "82" printed in white ink.

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

LAGEVRIO is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients and caregivers, respectively, through Merck's website www.molnupiravir.com (referred to as the "authorized labeling"):

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[11] 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.

[12] Patients requiring hospitalization after starting treatment with molnupiravir may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

RETURN TO PACKAGE TABLE

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for LAGEVRIO
- Fact Sheet for Patients and Caregivers: Emergency Use Authorization (EUA) of LAGEVRIO 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 LAGEVRIO, when used for the treatment of adults with a current diagnosis of mild-to-moderate 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 LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate 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 LAGEVRIO (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 LAGEVRIO product 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), LAGEVRIO is authorized for the treatment of adults with a current diagnosis of mild-to-moderate 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:

Merck and Authorized Distributors[14]

A. Merck and authorized distributor(s) will ensure that LAGEVRIO is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. Merck and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Merck 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

[14] Supra at Note 10.

RETURN TO PACKAGE TABLE

government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving LAGEVRIO. Merck 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. Merck may request changes to this authorization, including to the authorized Fact Sheets for LAGEVRIO. 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.[15]

E. Merck 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 LAGEVRIO 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 LAGEVRIO are prohibited. If the Agency notifies Merck that any instructional and educational materials are inconsistent with the authorized labeling, Merck must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

F. Merck will report to FDA all serious adverse events and medication errors potentially related to LAGEVRIO use that are reported to Merck 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: "LAGEVRIO 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.

[15] 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.

RETURN TO PACKAGE TABLE

G. 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.

H. Merck will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of LAGEVRIO 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.

Merck 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, Merck must recall them.

If not included in its initial notification, Merck must submit information confirming that Merck 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. Merck must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Merck will manufacture LAGEVRIO to meet all quality standards and per the manufacturing process and control strategy as detailed in Merck's EUA request. Merck will also test the active pharmaceutical ingredient (API) starting material for additional quality attributes agreed upon by Merck and the Agency. Merck 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. Merck will list LAGEVRIO 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.

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

RETURN TO PACKAGE TABLE

L. Merck will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. Merck 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.

M. FDA may require Merck to assess the activity of the authorized LAGEVRIO 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). Merck will perform the required assessment in a manner and timeframe agreed upon by Merck and the Agency. Merck 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. Merck 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.

N. Merck shall provide samples as requested of LAGEVRIO to the U.S. Department of Health and Human Services (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 LAGEVRIO may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

O. Merck must provide the following information to the Agency:

1. Merck will conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of trial MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. Merck will submit a final report, including available serology results, to the Agency no later than September 30, 2022.
2. Merck will conduct a pharmacokinetic (PK) study in wild type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Merck will submit the results of the PK study no later than March 31, 2022.

    - If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, Merck will also conduct a male germ cell mutation assay in the Big Blue rat model. Merck must submit a protocol for the Big Blue rat assay no later than 30 days after the PK results are submitted to FDA, or by April 30, 2022. Results from the Big Blue rat assay will be submitted no later than July 31, 2023.

RETURN TO PACKAGE TABLE

P. Merck must participate in a pregnancy registry to collect information through telephone and online reporting of pregnancies and collect outcomes for individuals who are exposed to LAGEVRIO during pregnancy. Merck must submit to the Agency reports detailing any available exposure information and outcome(s) data on a monthly basis unless otherwise notified by FDA.

Q. Merck and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom LAGEVRIO Is Distributed and Healthcare Providers Administering LAGEVRIO

R. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein. Healthcare providers must provide and document that a copy of the authorized Fact Sheet for Patients and Caregivers has been provided, either through electronic means or hardcopy, to the patient or caregiver prior to prescribing LAGEVRIO.

S. Healthcare providers must inform patients or caregivers of the information detailed in the section *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

T. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has completed the mandatory requirements on patient assessment, patient counseling, and documentation as described in the Fact Sheet for Healthcare Providers. See *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

U. Healthcare providers must inform and document that pregnant individuals who are prescribed LAGEVRIO have been made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

V. Healthcare facilities and healthcare providers receiving LAGEVRIO will track all serious adverse events and medication errors that are considered to be potentially related to LAGEVRIO 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 must state, "LAGEVRIO use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

W. 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.

RETURN TO PACKAGE TABLE

X. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of LAGEVRIO 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).

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

Z. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

AA. All descriptive printed matter, advertising, and promotional materials relating to the use of LAGEVRIO 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 LAGEVRIO 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.

BB. Merck may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of LAGEVRIO 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. Merck may not imply that LAGEVRIO is FDA-approved for its authorized use by making statements such as "LAGEVRIO is safe and effective for the treatment of COVID-19."

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

RETURN TO PACKAGE TABLE

- LAGEVRIO has not been approved, but has been authorized for emergency use by FDA under an EUA, 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; and

- The emergency use of LAGEVRIO 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 Merck that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions AA through CC of this EUA, Merck 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 Merck 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,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2023.02.01 10:20:45 -05'00'

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

RETURN TO PACKAGE TABLE

Document 3C.5

U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19

Document URL

https://www.fda.gov/media/155056/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19

Q: What is an emergency use authorization (EUA)?
A: Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q: What does this EUA authorize? What are the limitations of authorized use?
A: FDA has issued an EUA for the emergency use of the unapproved product Lagevrio (molnupiravir) 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 alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Lagevrio is not FDA-approved for any use including for the treatment of COVID-19. Prior to initiating treatment with Lagevrio, carefully consider the known and potential risks and benefits.

Lagevrio is not authorized:

- for use in patients less than 18 years of age.
- for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with Lagevrio has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- for use for longer than five consecutive days.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q: How is high risk defined under the EUA?
A: Information about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention's People with Certain Medical Conditions website. Health care providers should consider the benefit-risk for an individual patient.

Q: Does the EUA require a positive result from a direct SARS-CoV-2 viral test prior to prescribing Lagevrio to a patient who is at high risk for severe COVID-19?"
A: No. Although the Agency continues to recommend that authorized prescribers use direct SARS-CoV-2 viral testing to help diagnose COVID-19, the Agency removed the requirement for positive test results effective February 1, 2023. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact with a positive direct SARS-CoV-2 viral test) who develop signs and symptoms consistent with COVID-19 may be diagnosed by an authorized prescriber as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, the authorized prescriber may determine that treatment with Lagevrio for COVID-19 is appropriate if the patient

reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Healthcare Providers.

Q: What does direct SARS-CoV-2 viral testing mean?
A: Direct SARS-CoV-2 viral tests diagnose current COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q: Are there any warnings or precautions that should be taken when administering Lagevrio?
A: Yes, health care providers and patients must be aware of the following warnings and precautions:

- Pregnancy
  Lagevrio may cause fetal harm when administered to pregnant individuals. Therefore, **Lagevrio is not recommended for use during pregnancy.** Prior to initiating treatment with Lagevrio, health care providers should assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Lagevrio is authorized to be prescribed to a pregnant individual only after the health care provider has determined that the benefits would outweigh the risks for that individual patient and the known and potential benefits and potential risks of using Lagevrio during pregnancy are communicated to the pregnant individual.

- Lactation
  Breastfeeding is not recommended during treatment with Lagevrio and for four days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of Lagevrio.

- Females of Reproductive Potential
  Females of childbearing potential are advised to use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.

- Males of Reproductive Potential
  While the risk is regarded as low, studies to fully assess the potential for Lagevrio to affect offspring of treated males have not been completed. Sexually active individuals with partners of childbearing potential are advised to use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose of Lagevrio. The risk beyond three months after the last dose of Lagevrio is unknown. Studies to understand the risk beyond three months are ongoing.

- Hypersensitivity Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with Lagevrio. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Lagevrio and initiate appropriate medications and/or supportive care.

Q: Are there potential side effects of Lagevrio?
A: Possible side effects of Lagevrio include diarrhea, nausea, and dizziness. Lagevrio is not recommended for use during pregnancy because findings from animal reproduction studies showed that Lagevrio may cause fetal harm when administered to pregnant individuals.

Hypersensitivity, anaphylaxis, angioedema, erythema, rash, and urticaria adverse reactions have been identified during post-authorization use of Lagevrio.

Q: Why is Lagevrio only authorized in adults?
A: Lagevrio is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

Q: Is Lagevrio approved by the FDA to prevent or treat COVID-19?
A: No. Lagevrio is not FDA-approved to prevent or treat any diseases or conditions, including COVID-19. Lagevrio is an investigational drug.

Q: How can Lagevrio be obtained for use under the EUA?
A: For questions on how to obtain Lagevrio, please contact COVID19therapeutics@hhs.gov.

Q. Who may prescribe Lagevrio under the EUA?
A. Under the authorization, Lagevrio may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Lagevrio belongs (i.e., anti-infectives).

Q: When should Lagevrio be administered to a patient?
A: Patients should talk to their healthcare provider to determine whether, based on their individual circumstances and whether alternative COVID-19 treatment options approved or authorized by FDA are accessible or clinically appropriate, they are eligible to receive Lagevrio. Patients should take Lagevrio as soon as possible after a diagnosis of COVID-19 has been made, and within five days of symptom onset.

More information about administration is available in the Fact Sheet for Health Care Providers.

Q: Does the EUA permit the use of Lagevrio as authorized in patients hospitalized *for reasons other* than COVID-19?
A: If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient has a current diagnosis of mild-to-moderate COVID-19, then treatment with Lagevrio is authorized if the patient is also at high risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met as detailed in the Fact Sheet for Health Care Providers.

Lagevrio is also authorized for patients who require hospitalization after starting treatment with Lagevrio. These patients may complete the full five-day treatment course per the health care provider's discretion.

Q: Are there data showing treatment with Lagevrio may benefit adults with mild-to-moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization?
A: Yes. The most important scientific evidence supporting the authorization of Lagevrio is from MOVe-OUT, a randomized, placebo-controlled, double-blind clinical trial studying Lagevrio for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within five days of randomization.

The main outcome measured in the trial was the percentage of people who were hospitalized or died due to any cause during 29 days of follow-up. Of the 709 people who received Lagevrio, 6.8% were hospitalized or died within this time period compared to 9.7% of the 699 people who received a placebo. This represented an adjusted relative risk reduction of Lagevrio compared to placebo of approximately 30% for all those randomized. Of the people who received Lagevrio, one died within this time period compared to nine people who received a placebo. The safety and effectiveness of Lagevrio for the treatment of COVID-10 continue to be evaluated.

Q: Are there requirements for health care facilities and prescribing health care providers as part of the EUA?
A: Yes.

- As part of the EUA, FDA requires health care providers who prescribe Lagevrio to report all medication errors and serious adverse events considered to be potentially related to Lagevrio through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Merck Sharp & Dohme Corp.
- Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.
- Healthcare providers must provide an electronic or hard copy of the "Fact Sheet for Patients, and Caregivers" prior to the patient receiving Lagevrio and must document that the patient has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".
- Healthcare providers must inform the patient or caregiver that:
    - Lagevrio is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    - 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].
    - There are benefits and risks of taking Lagevrio as outlined in the "Fact Sheet for Patients and Caregivers."
    - There is a pregnancy registry for patients exposed to Lagevrio.

    - Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.
    - Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose.
- The prescribing health care provider must assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
- Based on findings from animal reproduction studies, Lagevrio may cause fetal harm when administered to pregnant individuals. If Lagevrio is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers".
- If the decision is made to use Lagevrio during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.
- There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to Lagevrio during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to Lagevrio or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Q: Do patient outcomes need to be reported under the EUA?
A: No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Lagevrio occurring during treatment is required.

Q: FDA has issued a number of EUAs, including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?
A: As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q: Can health care providers share the patient/caregiver fact sheet electronically?
A: Yes. The letter of authorization for Lagevrio authorizes healthcare providers to share the patient/caregiver fact sheet electronically.

RETURN TO PACKAGE TABLE

Document 3C.6

U.S. FDA Molnupiravir checklist tool for prescribers

Document URL

https://www.fda.gov/media/155118/download

Reference website URL

https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

License

Not applicable

RETURN TO PACKAGE TABLE

Molnupiravir Checklist Tool for Prescribers:

Patient Eligibility

Patient Name: _____ DOB:_____

- ❑ Current diagnosis of mild to moderate COVID-19[1]
- ❑ Age ≥ 18 years
- ❑ Alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate
- ❑ High risk criteria[2] met
- ❑ Symptom onset within 5 days*
- ❑ Not hospitalized due to COVID-19

*Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by _____[insert date]_____. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.

[1] https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Patients%20with%20mild%20illness%20may,on%20exertion%2C%20or%20abnormal%20imaging

[2] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

RETURN TO PACKAGE TABLE

Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements

1. All Patients

- ❑ Provide electronic or hard copy of patient fact sheet
  - ❑ Document that patient has received an electronic or hard copy of the patient fact sheet[3]
  - ❑ Review the information contained within the patient factsheet with the patient and counsel patient on the known and potential benefits and risks of MOV
  - ❑ Advise patients on need for contraception use as appropriate
    - ❑ Females of childbearing potential treated: should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir
    - ❑ Males of reproductive potential treated: if sexually active with females of childbearing potential, should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose
  - ❑ The prescribing healthcare provider and/or the provider's designee must report all medication errors and serious adverse events potentially related to molnupiravir within 7 calendar days from the healthcare provider's awareness of the event

2. Individuals of Childbearing Potential

- ❑ Assess whether pregnant or not
  - ❑ Report of LMP in an individual who has regular menstrual cycles, uses a reliable method of contraception correctly and consistently or has had a negative pregnancy test
  - ❑ Negative pregnancy test (recommended but not required if other criteria are not met)
- ❑ If pregnant:
  - ❑ Counsel the patient regarding the known and potential benefits and potential risks of molnupiravir use during pregnancy
  - ❑ Document that the patient is aware of the known and potential benefits and potential risks of molnupiravir use during pregnancy
  - ❑ Make the individual aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791
- ❑ If not pregnant:
  - ❑ Make the individual aware of the pregnancy registry program and encourage them to participate should they become pregnant

[3] How and where documentation occurs is at the discretion of the prescribing health care provider and their clinical site.

RETURN TO PACKAGE TABLE

Document 3C.7

U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (March 23, 2022)

Document URL

https://www.fda.gov/media/157300/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

Not applicable

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., 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) [redacted]
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)

RETURN TO PACKAGE TABLE

Intended Population(s)	Adults with positive results of direct SARS-CoV-2 viral testing, and 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 Fact Sheets

The molnupiravir EUA fact sheets are being revised at this time for the following reasons:

1. The Division of Medication Error Prevention and Analysis recently concluded that the proprietary name for molnupiravir, LAGEVRIO, is conditionally acceptable. Therefore, the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients and Caregivers are being updated to reference the proprietary name for molnupiravir. Further, the Letter of Authorization is being reissued to reference the proprietary name for molnupiravir.
2. New data regarding the cell culture antiviral activity of the molnupiravir metabolite, N^4-hydroxycytidine (NHC), against an expanded panel of SARS-CoV-2 variants has recently become available. Section 12.4 Microbiology of the Fact Sheet for Healthcare Providers were be updated to include these data.

Summary of Fact Sheet Revisions

Throughout both Fact Sheets, the proprietary name, LAGEVRIO, has been added where appropriate. In addition, the following changes have been made:

FACT SHEET FOR HEALTHCARE PROVIDERS

Section 1 Emergency Use Authorization

~~Information Regarding Available Alternatives for the EUA Authorized Use~~APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of 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, 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 treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, 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 ~~molnupiravir~~LAGEVRIO for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for three days ~~3-day treatment duration~~).

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

Section 12.4 Microbiology

Antiviral Activity
NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC50 values) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1)~~, and~~ Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1 and BA.1.1), with EC50 values of 0.95-2.6 µM~~with EC50 values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively~~. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified. ~~NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.~~

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with molnupiravir compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance
NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir ~~sensitivity~~susceptibility, indicating a lack of cross-resistance.

RETURN TO PACKAGE TABLE

FACT SHEET FOR PATIENTS AND CAREGIVERS

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. Talk with your doctor to see if Veklury is appropriate for you.

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 LAVEVRIO. In addition, the Letter of Authorization is being reissued using the proprietary name. Lastly, the Dear Health Care Provider letter associated with this EUA is being revised to include the proprietary name and to update the authorized use statement to reflect changes made to the Authorized Use Statement on February 11, 2022.[1]

[1] The Letter of Authorization for molnupiravir was reissued on February 11, 2022, to account for the FDA-approval of Veklury (remdesivir) for the treatment of 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, 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. The text in bold was added to the Authorized Use Statement at that time:

> Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk 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.

RETURN TO PACKAGE TABLE

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use LAGEVRIO under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for LAGEVRIO.

LAGEVRIO™ (molnupiravir) capsules, for oral use
Original EUA Authorized Date: 12/23/2021
Revised EUA Authorized Date: 03/2022

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------RECENT MAJOR CHANGES----------

Mandatory Requirements Box: Revised requirements pertaining to other therapeutics	02/2022
Emergency Use Authorization (Section 1): Updates on available alternatives to LAGEVRIO	02/2022
Warnings and Precautions (Sections 5.2 and 17): addition of hypersensitivity including anaphylaxis	02/2022
Adverse Reactions (Section 6.2): addition of post-authorization experience section	02/2022

----------EUA FOR LAGEVRIO----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved LAGEVRIO, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing 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 is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- LAGEVRIO is not authorized
  - for use in patients less than 18 years of age (5.3)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescr bed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of LAGEVRIO under emergency use authorization.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1)
- Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. (2.1)
- LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: LAGEVRIO is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO. (5.2)
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.3, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to LAGEVRIO (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of LAGEVRIO is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

RETURN TO PACKAGE TABLE

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of LAGEVRIO, the following steps are required. Use of LAGEVRIO under this EUA is limited to the following (all requirements must be met):

1. Treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, 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 *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving LAGEVRIO. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving LAGEVRIO and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    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].*
    iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
    iv. Merck Sharp & Dohme has established a pregnancy surveillance program.
    v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
    vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*

5. Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. If LAGEVRIO is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)].*

6. If the decision is made to use LAGEVRIO during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

RETURN TO PACKAGE TABLE

7. The prescribing healthcare provider must document that a pregnant individual was made aware of Merck Sharp & Dohme's pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com.
    a. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov .

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 mild-to-moderate COVID-19 in adults:

- with positive results of direct SARS-CoV-2 viral testing, and
- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.3)]*.
- LAGEVRIO is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is not approved for any use, including for use for the treatment of COVID-19.

Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

[1] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions html . Healthcare providers should consider the benefit-risk for an individual patient.
[2] Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

RETURN TO PACKAGE TABLE

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - 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 biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of 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, 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 treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, 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 practical for certain patients (e.g., it requires an intravenous infusion daily for three days).

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of LAGEVRIO in Adult Patients

RETURN TO PACKAGE TABLE

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Patient Counseling Information (17)]*.

LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

If the patient misses a dose of LAGEVRIO within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for LAGEVRIO. Serious and unexpected adverse events may occur that have not been previously reported with LAGEVRIO use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended for use during pregnancy. When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with LAGEVRIO and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

RETURN TO PACKAGE TABLE

Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Hypersensitivity Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS
6.1 Adverse Reactions from Clinical Studies
The following adverse reactions have been observed in the clinical study of LAGEVRIO that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with LAGEVRIO may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to LAGEVRIO 800 mg twice daily in clinical trials. The safety assessment of LAGEVRIO is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of LAGEVRIO was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with LAGEVRIO (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving LAGEVRIO and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving LAGEVRIO and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving LAGEVRIO and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the LAGEVRIO treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving LAGEVRIO in MOVe-OUT*

	LAGEVRIO N=710	**Placebo N=701**
Diarrhea	2%	2%
Nausea	1%	1%

RETURN TO PACKAGE TABLE

Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities
Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVe-OUT.

6.2 Post-Authorization Experience
The following adverse reactions have been identified during post-authorization use of LAGEVRIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders
hypersensitivity, anaphylaxis, angioedema *[see Warnings and Precautions (5.2)]*

Skin and Subcutaneous Tissue Disorders
erythema, rash, urticaria

6.4 Required Reporting for Serious Adverse Events and Medication Errors
The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "*LAGEVRIO* use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

RETURN TO PACKAGE TABLE

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of LAGEVRIO.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

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.

7 DRUG INTERACTIONS
No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. No clinical drug-drug interaction trials of LAGEVRIO with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Surveillance Program
There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of Merck Sharp & Dohme's pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme. Pregnant individuals exposed to LAGEVRIO can also report the exposure by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com.

Risk Summary
Based on animal data, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO

RETURN TO PACKAGE TABLE

during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from LAGEVRIO, breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1, 5.3)].*

Data

When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

RETURN TO PACKAGE TABLE

8.3 Females and Males of Reproductive Potential
Based on animal studies, LAGEVRIO may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing
Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)].*

Contraception
Females
Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1)].*

Males
While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of LAGEVRIO.
The risk beyond three months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use
LAGEVRIO is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with LAGEVRIO. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

RETURN TO PACKAGE TABLE

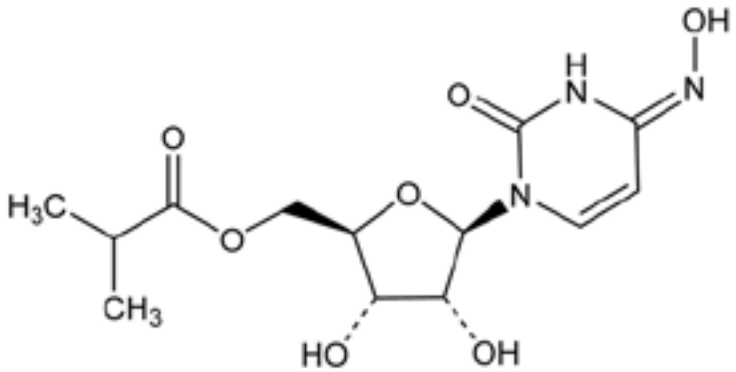
10 OVERDOSAGE

There is no human experience of overdosage with LAGEVRIO. Treatment of overdose with LAGEVRIO should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION

LAGEVRIO capsules contain molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5´-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each LAGEVRIO capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2 infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with LAGEVRIO.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is

RETURN TO PACKAGE TABLE

eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)
Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated. *Values were obtained from population PK analysis. †Median [min - max]	

Specific Populations

Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients

LAGEVRIO has not been studied in pediatric patients.

Patients with Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

Patients with Hepatic Impairment

The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies

In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP

RETURN TO PACKAGE TABLE

or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology

Antiviral Activity

NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.66 μM in A-549 cells and 0.32 to 2.03 μM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1 and BA.1.1),with EC_{50} values of 0.95-2.6 μM . NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance

No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating LAGEVRIO for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with LAGEVRIO compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance

NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir susceptibility, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models

The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity

NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 μM (human lymphoid CEM cell line) to >100 μM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 μM and 7.7 μM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A mouse carcinogenicity study with molnupiravir is ongoing.

Mutagenesis

RETURN TO PACKAGE TABLE

Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology
Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES
Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of LAGEVRIO or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-

RETURN TO PACKAGE TABLE

eight percent of subjects received LAGEVRIO or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

LAGEVRIO (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

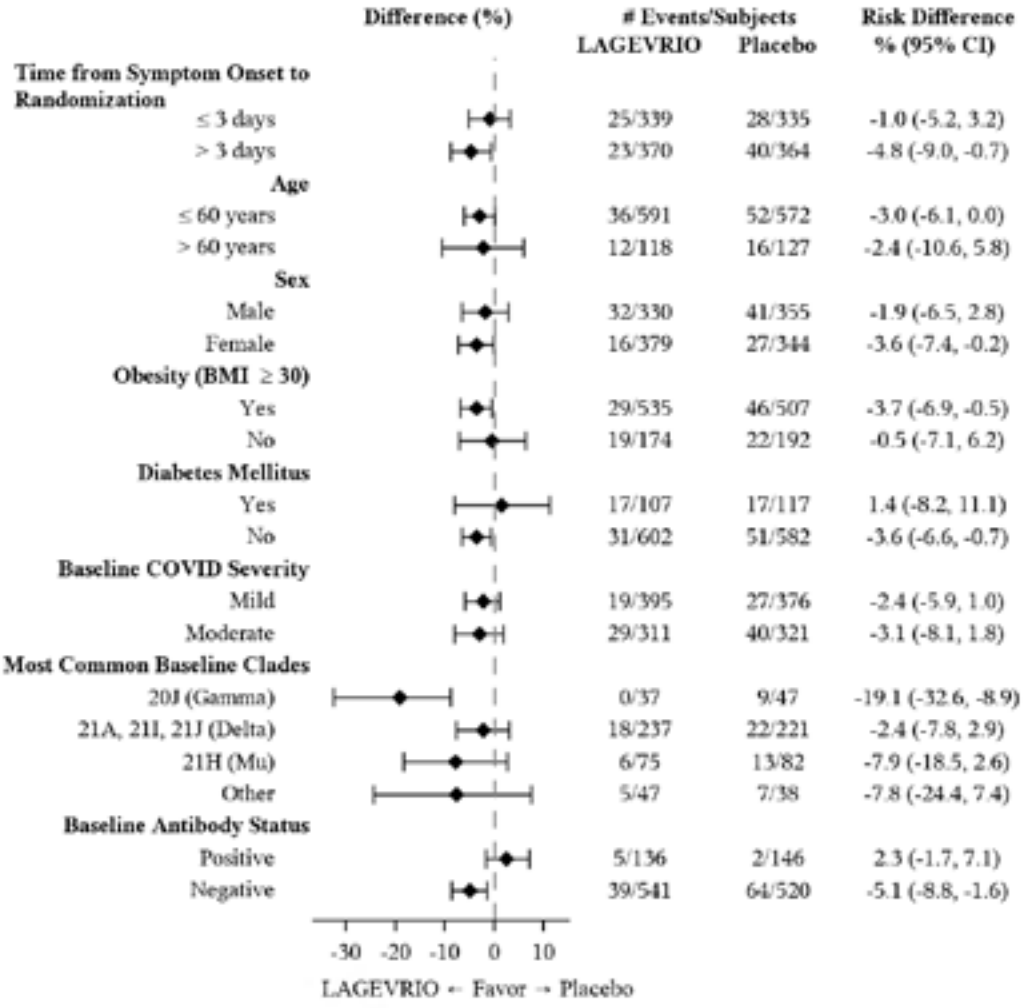
*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received LAGEVRIO were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of LAGEVRIO compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects

RETURN TO PACKAGE TABLE



The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC
200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and “82” printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07

Storage and Handling

Store LAGEVRIO capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

RETURN TO PACKAGE TABLE

As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving LAGEVRIO *[see Box]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have been reported, even following a single dose of LAGEVRIO, and to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

Risk of Fetal Toxicity
Advise patients that LAGEVRIO is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking LAGEVRIO and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking LAGEVRIO and for at least 3 months after the last dose of LAGEVRIO. The risk beyond 3 months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)].*

Risk of Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)].*

Pregnancy Surveillance Program
There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy surveillance program. Advise patients who have taken LAGEVRIO during pregnancy to report their pregnancy to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Advise lactating individuals to consider interrupting breastfeeding and to consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

RETURN TO PACKAGE TABLE

Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Dosage and Administration (2.2)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

For patent information: www.msd.com/research/patent

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RETURN TO PACKAGE TABLE

Fact Sheet for Patients And Caregivers
Emergency Use Authorization (EUA) Of LAGEVRIO™ (molnupiravir) capsules For Coronavirus Disease 2019 (COVID-19)

What is the most important information I should know about LAGEVRIO?
LAGEVRIO may cause serious side effects, including:

- **LAGEVRIO may cause harm to your unborn baby. It is not known if LAGEVRIO will harm your baby if you take LAGEVRIO during pregnancy.**
  - LAGEVRIO is not recommended for use in pregnancy.
  - LAGEVRIO has not been studied in pregnancy. LAGEVRIO was studied in pregnant animals only. When LAGEVRIO was given to pregnant animals, LAGEVRIO caused harm to their unborn babies.
  - You and your healthcare provider may decide that you should take LAGEVRIO during pregnancy if there are no other COVID-19 treatment options approved or authorized by the FDA that are accessible or clinically appropriate for you.
  - If you and your healthcare provider decide that you should take LAGEVRIO during pregnancy, you and your healthcare provider should discuss the known and potential benefits and the potential risks of taking LAGEVRIO during pregnancy.

For individuals who are able to become pregnant:

- You should use a reliable method of birth control (contraception) consistently and correctly during treatment with LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Talk to your healthcare provider about reliable birth control methods.
- Before starting treatment with LAGEVRIO your healthcare provider may do a pregnancy test to see if you are pregnant before starting treatment with LAGEVRIO.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LAGEVRIO.

Pregnancy Surveillance Program:

- There is a pregnancy surveillance program for individuals who take LAGEVRIO during pregnancy. The purpose of this program is to collect information about the health of you and your baby. Talk to your healthcare provider about how to take part in this program.
- If you take LAGEVRIO during pregnancy and you agree to participate in the pregnancy surveillance program and allow your healthcare provider to share your information with Merck Sharp & Dohme, then your healthcare provider will report your use of LAGEVRIO during pregnancy to Merck Sharp & Dohme Corp. by calling 1-877-888-4231 or pregnancyreporting.msd.com.

For individuals who are sexually active with partners who are able to become pregnant:

- It is not known if LAGEVRIO can affect sperm. While the risk is regarded as low, animal studies to fully assess the potential for LAGEVRIO to affect the babies of males treated with LAGEVRIO have not been completed. A reliable method of birth control (contraception) should be used consistently and correctly during treatment with LAGEVRIO and for at least 3 months after the last dose. The risk to sperm beyond 3 months is not known. Studies to understand the risk to sperm beyond 3 months are ongoing. Talk to your healthcare provider

RETURN TO PACKAGE TABLE

about reliable birth control methods. Talk to your healthcare provider if you have questions or concerns about how LAGEVRIO may affect sperm.

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 mild-to-moderate coronavirus disease 2019 (COVID-19) with positive results of direct SARS-CoV-2 viral testing, and 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.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make LAGEVRIO available during the COVID-19 pandemic (for more details about an EUA please see **"What is an Emergency Use Authorization?"** at the end of this document). LAGEVRIO is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about LAGEVRIO. Talk to your healthcare provider about your options if you have any questions. It is your choice to take LAGEVRIO.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is LAGEVRIO?
LAGEVRIO is an investigational medicine used to treat mild-to-moderate COVID-19 in adults:

- with positive results of direct SARS-CoV-2 viral testing, and
- 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.

The FDA has authorized the emergency use of LAGEVRIO for the treatment of mild-to-moderate COVID-19 in adults under an EUA. For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

LAGEVRIO is not authorized:

- for use in people less than 18 years of age.
- for prevention of COVID-19.
- for people needing hospitalization for COVID-19.
- for use for longer than 5 consecutive days.

What should I tell my healthcare provider before I take LAGEVRIO?

RETURN TO PACKAGE TABLE

Tell your healthcare provider if you:

- Have any allergies
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products).

How do I take LAGEVRIO?

- Take LAGEVRIO exactly as your healthcare provider tells you to take it.
- Take 4 capsules of LAGEVRIO every 12 hours (for example, at 8 am and at 8 pm)
- **Take LAGEVRIO for 5 days**. It is important that you complete the full 5 days of treatment with LAGEVRIO. Do not stop taking LAGEVRIO before you complete the full 5 days of treatment, even if you feel better.
- Take LAGEVRIO with or without food.
- You should stay in isolation for as long as your healthcare provider tells you to. Talk to your healthcare provider if you are not sure about how to properly isolate while you have COVID-19.
- Swallow LAGEVRIO capsules whole. Do not open, break, or crush the capsules. If you cannot swallow capsules whole, tell your healthcare provider.
- **What to do if you miss a dose:**
  - If it has been **less than 10 hours** since the missed dose, take it as soon as you remember
  - If it has been **more than 10 hours** since the missed dose, skip the missed dose and take your dose at the next scheduled time.
- Do not double the dose of LAGEVRIO to make up for a missed dose.

What are the important possible side effects of LAGEVRIO?

- See, **"What is the most important information I should know about LAGEVRIO?"**

- **Allergic Reactions.** Allergic reactions can happen in people taking LAGEVRIO, even after only 1 dose. Stop taking LAGEVRIO and call your healthcare provider right away if you get any of the following symptoms of an allergic reaction:
  - hives
  - rapid heartbeat
  - trouble swallowing or breathing
  - swelling of the mouth, lips, or face
  - throat tightness
  - hoarseness
  - skin rash

The most common side effects of LAGEVRIO are:

- diarrhea
- nausea
- dizziness

These are not all the possible side effects of LAGEVRIO. Not many people have taken LAGEVRIO. Serious and unexpected side effects may happen. This medicine is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?

RETURN TO PACKAGE TABLE

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

Like LAGEVRIO, FDA may also allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for more information.

It is your choice to be treated or not to be treated with LAGEVRIO. Should you decide not to take it, it will not change your standard medical care.

What if I am breastfeeding?
Breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the last dose of LAGEVRIO. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about your options and specific situation before taking LAGEVRIO.

How do I report side effects with LAGEVRIO?
Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088).

How should I store LAGEVRIO?

- Store LAGEVRIO capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep LAGEVRIO and all medicines out of the reach of children and pets.**

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit www.cdc.gov/COVID19
- Contact your local or state public health department.
- Call Merck Sharp & Dohme at 1-800-672-6372 (toll free in the U.S.)
- Visit 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 for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, 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, has not undergone the same type of review as an FDA-approved product. 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.

RETURN TO PACKAGE TABLE

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for LAGEVRIO is in effect for the duration of the COVID-19 declaration justifying emergency use of LAGEVRIO, unless terminated or revoked (after which LAGEVRIO may no longer be used under the EUA).

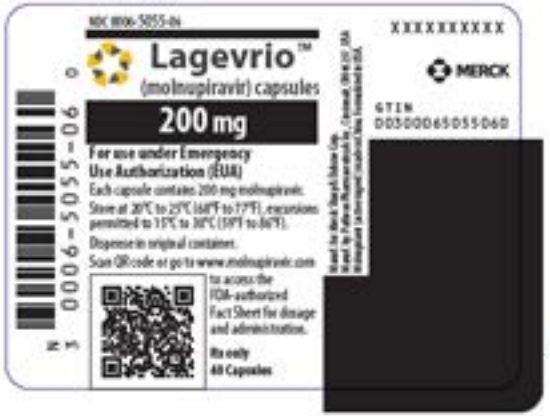
Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.msd.com/research/patent

usfsp-mk4482-c-2203r002

Revised: March 2022

RETURN TO PACKAGE TABLE



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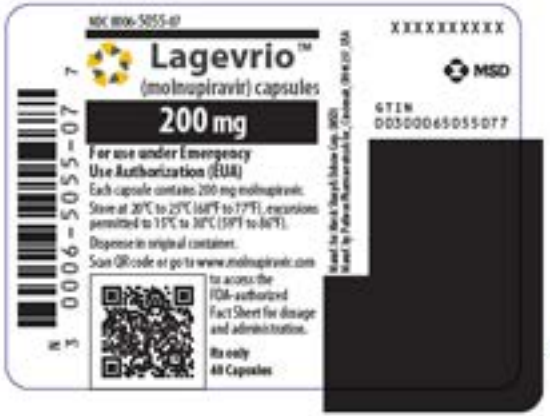

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/s/

DAVID E ARAOJO
03/23/2022 12:17:02 PM

KIMBERLY A STRUBLE
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DEBRA B BIRNKRANT
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JOHN J FARLEY
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RETURN TO PACKAGE TABLE

Document 3C.8

U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)

Document URL

https://www.fda.gov/media/165228/download

Reference website URL

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological

License

Not applicable

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., 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.

RETURN TO PACKAGE TABLE

Rationale for Revisions to EUA Fact Sheets

The molnupiravir EUA fact sheets are being revised at this time for the following reasons:

1. **To revise the Emergency Use Authorization statement to remove the requirement for a positive result of direct SARS-CoV-2 viral testing.**

   The Agency has determined the wording "with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing" is not needed for Section 1: Emergency Use Authorization. We are removing the requirement for a positive result of direct SARS-CoV-2 viral testing to provide flexibility in making a clinical diagnosis of COVID-19 in some scenarios where doing so may be appropriate. However, we continue to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

   While a positive direct SARS-CoV-2 viral test generally should be available as part of diagnosing a patient with mild to moderate COVID-19, the sensitivity of antigen testing is lower than RT-PCR testing and in rare cases, timing of the availability of testing may justify making a diagnosis of COVID-19 prior to the availability of a positive test result. For example, a patient at high risk for disease progression and death presents with symptoms consistent with COVID-19, has a known exposure such as another person in the household with a positive direct SARS-CoV-2 viral test, but the patient has a negative antigen test and is awaiting RT-PCR results.

   In a study by Chu et al., among 225 adults and children with RT-PCR confirmed SARS-CoV-2 infection, antigen test sensitivity was 64% when compared with same-day RT-PCR. Antigen test sensitivity peaked on day 4 of illness at 77%.[1] Therefore, it is important to allow healthcare providers flexibility to consider the clinical context to aid in early COVID-19 diagnosis. This may be especially important for immunocompromised patients who may be at particularly high risk for progression to severe disease in the absence of timely treatment initiation.

   This change to the Emergency Use Authorization statement necessitates revisions to the Letter of Authorization and to the Prescriber Checklist in addition to updates to the Fact Sheets.

2. **To update the information on VEKLURY in the Fact Sheet for Healthcare Providers**

[1]Chu VT, Schwartz NG, and Donnelly MAP. Comparison of home antigen testing with RT-PCR and viral culture during the course of SARS-CoV-2 infection. *JAMA Intern Med.* 2022;182(7):701-709.

RETURN TO PACKAGE TABLE

With this update, the information regarding available alternatives for the EUA authorized use has been updated in relation to VEKLURY (remdesivir) to align with the most recent VEKLURY USPI.

3. **To add the results of the 6-month oral carcinogenicity study in RasH2 transgenic mice to Section 13.2 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the Fact Sheet for Healthcare Providers.**

   Previously, molnupiravir (MOV) was found to be positive in the Ames reverse mutation assay and equivocal in the Pig-a mutation assay but negative in the Big Blue transgenic rat mutation assay. Further, MOV was not found to be clastogenic in in vitro and in vivo micronucleus assays. A 26-week carcinogenicity study in Tg rasH2 transgenic male and female mice treated with 30, 100 and 300 mg/kg/day by oral gavage did not identify any drug-related neoplastic or non-neoplastic lesions. A statistically significant (p=0.0355) increasing trend in tumor incidence for hemangiosarcomas in the spleen of females was noted through 300 mg/kg/day but was attributed to an unusually low concurrent control rate (0%) for the study. The incidence rate of 12% was also within the historical control rate (0-16%) for the laboratory, multiple laboratories owned by the CRO, and the literature. Thus, the finding was not considered MK-4482-related.

4. **To update Section 12.4 (Microbiology) of the Fact Sheet for Healthcare Providers to include additional Omicron subvariants.**

   Updated nonclinical virology data submitted to the EUA continue to indicate that NHC, the nucleoside analogue metabolite of molnupiravir, has reasonably consistent cell culture antiviral activity against major SARS-CoV-2 variants tested to date. In the most recent analyses (summarized in study report PD020, received 9/29/2022, SDN 139), mean NHC EC_{50} values across different experiments for viruses representative of the Omicron sub-lineages BA.2, BA.4 and BA.5 were 3.0 μM, 1.8 μM and 0.55 μM, respectively. Minor edits to this section of the fact sheet are recommended to round EC_{50} values to 2 significant digits.

5. **To update the Mandatory Requirements Box and Sections 8 and 17 of the Fact Sheet for Healthcare Providers, as well as the Fact Sheet for Patients and Caregivers and the Dear Healthcare Provider Letter, to reflect a switch from using Merck's pregnancy surveillance program to using the COVID-PR International Drug Pregnancy Registry to collect data on exposures to molnupiravir in pregnancy.**

   Very limited data on pregnancy exposures have been collected to date via Merck's pregnancy surveillance program. The majority of patients reported to the surveillance program have been lost to follow-up. Therefore, Merck has agreed

RETURN TO PACKAGE TABLE

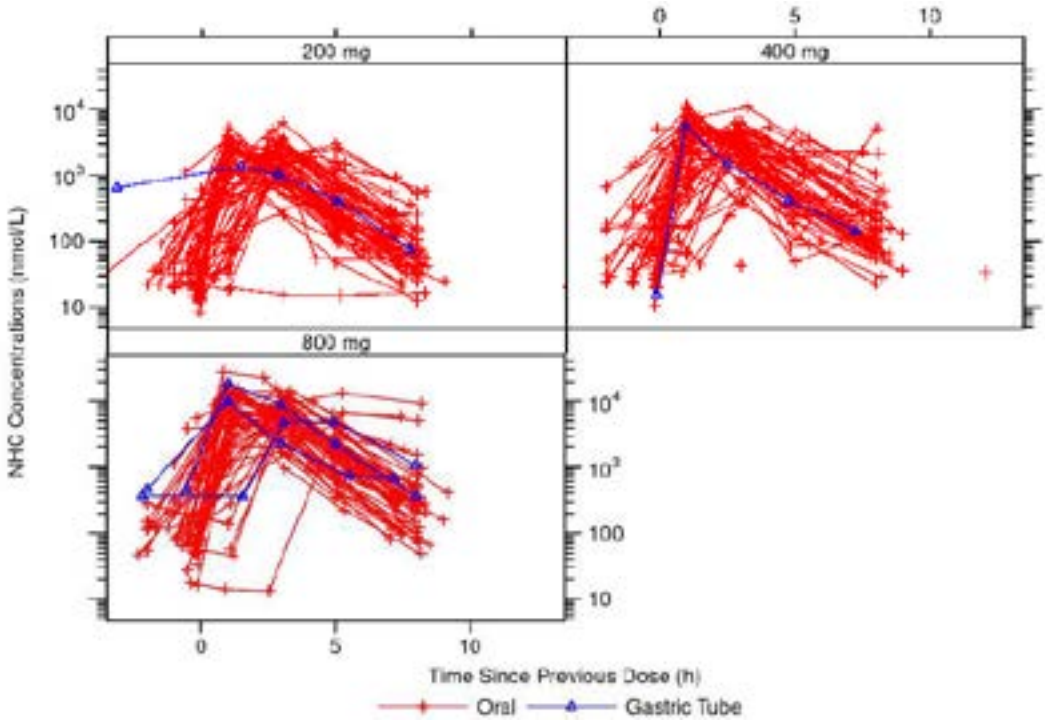
to participate in an existing pregnancy registry, the COVID-PR International Drug Pregnancy Registry, to collect pregnancy exposure and outcomes data moving forward.

In addition to updating the Fact Sheets to reflect this change in the mechanism for pregnancy exposure reporting, conditions P and U of the Letter of Authorization have also been revised accordingly.

6. **To include information regarding molnupiravir administration via nasogastric tubes and orogastric tubes to the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients and Caregivers.**

   In response to our comments regarding administering molnupiravir via a feeding tube (Responses to IR received on 12/16/2022, SDN150 and 1/9/2023, SDN153), Merck provided the comparison of plasma NHC PK between patients receiving MOV as oral capsules and via nasogastric or orogastric (NG/OG) tube. A total of 5 participants out of the 304 participants who enrolled in Study P001 received at least one dose of MOV via NG/OG tube. One subject was on 200 mg BID dose, one subject was on 400 mg BID dose, and 3 were on 800 mg BID dose. Data to distinguish between NG and OG tube administration were not collected; therefore, it cannot be specified how doses were received (NG or OG) for each individual participant. PK samples were collected following the last dose of MOV. It appears that plasma NHC concentrations following administration of MOV via NG/OG tube fell within the range of NHC concentrations following oral MOV capsule administration for all three dose levels (Figure 1). As such, the submitted information support updating the factsheets to include administration of MOV via NG/OG tube from a Clinical Pharmacology perspective.

Figure 1. NHC concentrations from samples taken following oral MOV administration compared to samples taken following MOV administration via nasogastric or orogastric tube.



Source: Responses to IR received on 12/16/2022, SDN150.

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 Dear Healthcare Provider Letter, the Frequently Asked Questions Document and the Prescriber Checklist 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.

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

Numbers 1, 3 and 7 in the Mandatory Requirements Box have been updated as follows:

1. Treatment of adults with a current diagnosis of mild-to-moderate COVID-19 ~~in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing,~~ 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 [see Limitations of Authorized Use (1)].

3. The prescribing healthcare providers must inform the patient/caregiver that:

RETURN TO PACKAGE TABLE

i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
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].*
iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
iv. ~~Merck Sharp & Dohme has established~~There is a pregnancy ~~surveillance program~~registry.
v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

7. The prescribing healthcare provider must document that a pregnant individual was made aware of ~~Merck Sharp & Dohme's~~the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791~~1-877-888-4231 or pregnancyreporting.msd.com~~.
   a. ~~If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme.~~

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 COVID-19 ~~in adults~~:

- ~~with positive results of direct SARS-CoV-2 viral testing, and~~[2]
- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website[3] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

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) ~~with positive results of direct SARS-CoV-2 viral testing,~~ 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 treatment of mild-to-moderate COVID-19 in adults ~~with positive results of direct SARS-CoV-2 viral testing, 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 ~~practical~~clinically appropriate for certain patients ~~(e.g., it requires an intravenous infusion daily for three days)~~.

[2] The indication was updated throughout both the HCP Factsheet and the Patient Factsheet to remove the requirement for positive results of direct SARS-CoV-2 viral testing.

[3] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

RETURN TO PACKAGE TABLE

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

2 DOSAGE AND ADMINISTRATION

2.3 Administration via Nasogastric (NG) or Orogastric (OG) tube (12F or Larger)

- Open four (4) capsules and transfer contents into a clean container with a lid.
- Add 40 mL of water to the container.
- Put the lid on the container and shake to mix the capsule contents and water thoroughly for 3 minutes.
  - **NOTE**: Capsule contents may not dissolve completely.
  - The prepared mixture may have visible undissolved particulates and are acceptable for administration.
- Flush NG/OG tube with 5 mL of water prior to administration.
- Using a catheter tip syringe, draw up the entire contents from the container and administer immediately through the NG/OG tube (12F or larger). Do not keep the mixture for future use.
- If any portion of the capsule contents are left in the container, add 10 mL of water to the container, mix, and using the same syringe draw up the entire contents of the container and administer through the NG/OG (12F or larger). Repeat as needed until no capsule contents are left in the bottle or syringe.
- Flush the tube with 5 mL of water twice (10 mL total) after administration of the mixture.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy ~~Surveillance Program~~Registry

There is a pregnancy ~~surveillance program~~registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the~~Merck Sharp & Dohme's~~ pregnancy ~~surveillance program~~registry at https://covid-pr.pregistry.com or 1-800-616-3791~~1-877-888-4231 or pregnancyreporting.msd.com. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme~~. Pregnant individuals exposed to LAGEVRIO or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231 or ~~pregnancyreporting.msd.com~~.

12.3 Pharmacokinetics

Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Plasma NHC concentrations in patients (N=5) following administration of molnupiravir via nasogastric or orogastric tube fell within the range of NHC concentrations following oral molnupiravir capsule administration under the same dosing regimen.

12.4 Microbiology

Antiviral Activity

RETURN TO PACKAGE TABLE

NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 (USA-WA1/~~2022~~2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, ~~and~~ BA.1.1, BA.2, BA.4 and BA.5), with mean EC_{50} values of 0.~~95~~5-2.~~69~~5 µM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

~~A mouse carcinogenicity study with molnupiravir is ongoing.~~Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC
200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and “82” printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07 NDC-0006-5055-09

17 PATIENT COUNSELING INFORMATION

Pregnancy ~~Surveillance Program~~Registry

There is a pregnancy registry~~surveillance program~~ that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy ~~surveillance program~~registry at https://covid-pr.pregistry.com or 1-800-616-3791. ~~Advise patients who have taken LAGEVRIO during pregnancy to report their pregnancy to Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com~~ [see Use in Specific Populations (8.1)].

Administration Instructions

Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

LAGEVRIO capsule contents can be mixed with water and given via nasogastric/orogastric tube. Inform patients to follow the instructions as described in the fact sheet for patients and caregivers *[see Dosage and Administration (2.3)]*.

FACT SHEET FOR PATIENTS AND CAREGIVERS

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

Pregnancy ~~Surveillance Program~~Registry:

RETURN TO PACKAGE TABLE

- There is a pregnancy ~~surveillance program~~registry for individuals who take LAGEVRIO during pregnancy. The purpose of this program is to collect information about the health of you and your baby. ~~Talk to your healthcare provider about how to take part in this program.~~
- If you are pregnant or become pregnant during treatment with ~~take~~ LAGEVRIO, ~~during pregnancy and~~ you ~~agree to participate in the pregnancy surveillance program and allow your healthcare provider to share your information with Merck Sharp & Dohme, then your healthcare provider will~~are encouraged to report your use of LAGEVRIO during pregnancy at https://covid-pr.pregistry.com or 1-800-616-3791 ~~to Merck Sharp & Dohme LLC. by calling 1-877-888-4231 or pregnancyreporting.msd.com~~.

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) ~~with positive results of direct SARS-CoV-2 viral testing, and~~ 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 is LAGEVRIO?

LAGEVRIO is an investigational medicine used to treat adults with a current diagnosis of mild-to-moderate COVID-19 ~~in adults:~~

- ~~with positive results of direct ARS-CoV-2 viral testing, and~~
- 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.

How do I take LAGEVRIO?

- If your healthcare provider prescribes LAGEVRIO and tells you to take or give a dose through a nasogastric (NG) or orogastric (OG) tube, follow the instructions below: "**How to take or give a dose of LAGEVRIO through a nasogastric (NG) or orogastric (OG) feeding tube**." You must have an NG or OG that is size 12 French (FR) or larger.

How to take or give a dose of LAGEVRIO through a nasogastric (NG) or orogastric (OG) feeding tube:

- Wash your hands well with soap and water.
- Gather the supplies you will need to take or give the prescribed dose of LAGEVRIO.
  - 4 LAGEVRIO capsules
  - 1 liquid measuring cup with mL markings to measure 40 mL of room temperature water
  - 1 clean container with a lid
  - 1 catheter tip syringe. Your healthcare provider should tell you what size catheter tip syringe you will need to take or give a dose of LAGEVRIO.
- Place the needed supplies on a clean work surface.
- Follow your healthcare provider's instructions on how to flush the NG or OG feeding tube. Flush the NG or OG feeding tube with **5 mL** of water before taking or giving a dose of LAGEVRIO.
- Carefully open 4 LAGEVRIO capsules, one at a time, and empty the contents into a clean container.

RETURN TO PACKAGE TABLE

- Use the liquid measuring cup to measure 40 mL of room temperature water and add to the container containing the capsule contents.
- Place the lid on the container. Shake to mix the capsule contents and water well for **3 minutes**. **The capsule contents may not dissolve completely.**
- Remove the lid from the container and draw up all the LAGEVRIO and water mixture into a catheter tip syringe.
- Give all of the mixture right away through the NG or OG feeding tube. **Do not keep the mixture for future use**.
- **If any capsule contents are left in the container**:
    - Add 10 mL of water to the container, and mix to loosen any capsule contents that are left in the container.
    - Use the catheter tip syringe to draw up all of the mixture in the container.
    - Give the mixture through the NG or OG feeding tube.
    - Repeat this process as needed until you no longer see any capsule contents left in the container or catheter tip syringe.
- Use the same catheter tip syringe to flush the NG or OG feeding tube 2 times with 5 mL of water (10mL total).
- Rinse the container, lid and catheter tip syringe well with clean water after use. Place on a clean paper towel until next use.

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.

RETURN TO PACKAGE TABLE

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/s/

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