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.

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.

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

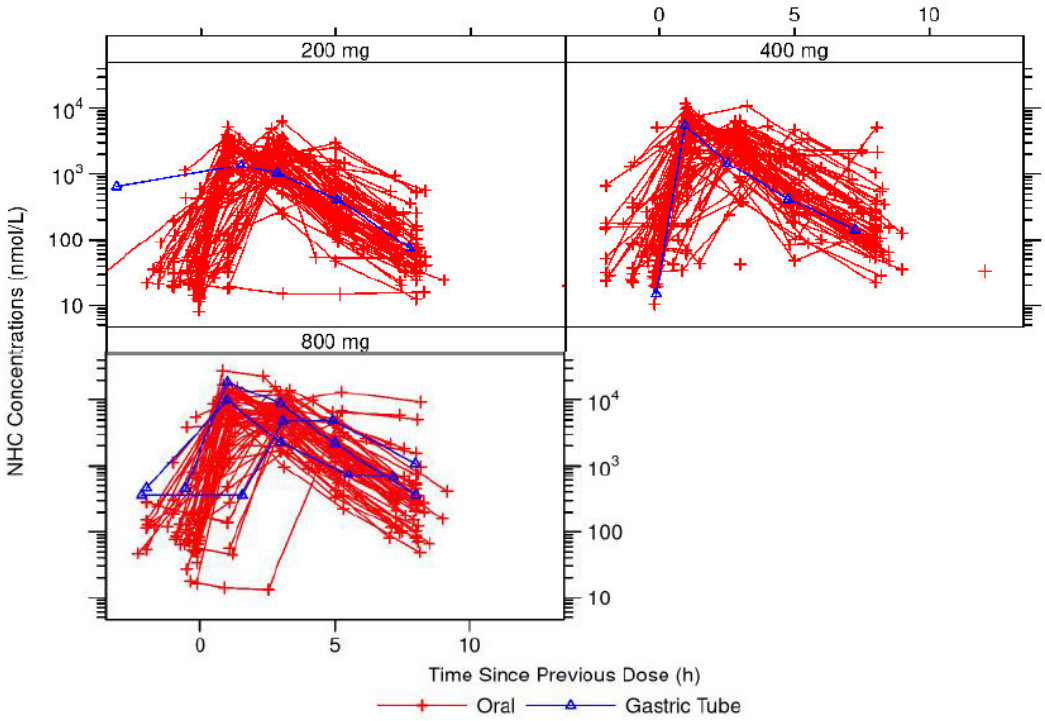
to participate in an existing pregnancy registry, the COVID-PR International Drug Pregnancy Registry, to collect pregnancy exposure and outcomes data moving forward.

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:

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.

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

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:

- 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.

- 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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