

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 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	n/a
Established Name/Other names used during development	Molnupiravir (MK-4482; MOV; EIDD-2801)
Dosage Forms/Strengths	Oral capsule, 200 mg
Therapeutic Class	SARS-CoV2 antiviral
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)

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.
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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 (MOV) EUA factsheets are being revised at this time for the following two reasons:

1. To account for the FDA approval of Veklury for an indication that overlaps with the MOV authorized use.

MOV was initially authorized for emergency use on December 23, 2021 for the treatment of mild-to-moderate COVID-19 in adults with positive results of 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 authorized by FDA are not accessible or clinically appropriate. At that time, there were several other therapeutics that were available under EUA, but not FDA-approved, for uses that overlap with the authorized use for MOV.

Subsequently, on January 21, 2022, FDA approved a supplemental new drug application (sNDA) to New Drug Application (NDA) 214787 for Veklury (remdesivir) for the treatment of adults and pediatric patients (12 years of age and older who weigh at least 40 kilograms, which is about 88 pounds) with positive results of direct SARS-CoV-2 viral testing, and who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.¹

As noted above, MOV was initially authorized for use only, in part, in adults for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. Given FDA's approval of the sNDA for Veklury as described above, prescribers should consider alternative COVID-19 treatment options that are either approved or authorized by FDA and whether they are accessible or clinically appropriate prior to prescribing MOV. Therefore, the authorized use statement will be revised to state that MOV is currently authorized for use only in adults for whom alternative COVID-19 treatment

¹ On October 22, 2020, FDA initially approved Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) requiring hospitalization. Veklury is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog ribonucleic acid (RNA) polymerase inhibitor.

options approved or authorized by FDA are not accessible or clinically appropriate.

Additionally, with FDA's approval of the sNDA described above, Veklury is an approved alternative to the MOV for its authorized use. However, FDA previously determined² that Veklury may not be an adequate alternative to MOV since Veklury must be administered via intravenous infusion over the course of 3 days, which may not be feasible or practical for certain patients. For example, it may not be possible for some patients to go to an infusion site for treatment for 3 days. The authorized Fact Sheets will also be revised to include language consistent with FDA's determination on this issue.

2. To add information regarding the post-authorization report of cases of hypersensitivity reactions and rash events in association with MOV use.

On February 2, 2022 DAV was made aware of 4 FAERS³ reports regarding hypersensitivity/anaphylaxis adverse events as well as 10 FAERS reports regarding rash, erythema, and urticaria adverse events in association with MOV use.

Hypersensitivity Adverse Events

Below is a summary of the four hypersensitivity reports.

- **FAERS #20334076**: A 58-year-old male with a past medical history of hypertension, diabetes mellitus, and kidney transplantation presented to the emergency department 30 minutes after starting MOV with throat swelling, chest pain, and dyspnea. This patient was reported to be taking several medications that are labeled for hypersensitivity and/or angioedema (e.g., sacubitril/valsartan, nifedipine, pravastatin and tacrolimus). However, the start dates for these concomitant medications were not provided. The outcome of this event is not reported.
- **FAERS #20363677**: A 77-year-old male with a past medical history of hypertension, polycystic kidney disease, and stage 5 chronic kidney disease received a 5-day course of MOV. Two days after finishing MOV, the patient presented to the emergency department with tongue and throat swelling and some difficulty breathing. This patient was reported to be taking several medications that are labeled for hypersensitivity and/or angioedema (e.g., amlodipine, lisinopril, simvastatin, and tamsulosin).

² See Memo to File to EUA 108 *Decision to maintain authorization of certain COVID-19 therapeutics following approval of sNDA for Veklury*, dated January 21, 2022.

³ The term "FAERS" refers to FDA's Adverse Event Reporting System.

However, the start dates for these concomitant medications were not provided. The outcome of this event is not reported.

- FAERS #20370267: An 85-year-old female with a past medical history of chronic renal failure, chronic cardiac failure, chronic obstructive pulmonary disease, and a liver disorder, experienced a decrease in systolic blood pressure (described as “usually 100-110 but decreased to the 70s”) and altered consciousness approximately one hour after taking MOV. This was classified by the reporting physician as anaphylaxis. An unspecified “infusion” was administered, MOV was stopped, and two days later the symptoms were resolved. No concomitant medications were reported.
- FAERS #20345235: A 67-year-old male with no reported medical history started MOV for the treatment of COVID-19. Four to five hours after the first MOV dose, the patient experienced “flash burn” type symptoms, described as intense burning with significant clear thin discharge in his eyes, nose and throat. These symptoms spontaneously resolved after four to five hours. MOV was stopped. No concomitant medications were reported.

The review team finds that with the exception of FAERS report 20363677 (in which the patient first developed symptoms 2 days after completing treatment with MOV) these cases are suggestive of MOV-associated hypersensitivity reactions. The potential role of MOV in these events is further supported by the positive de-challenge in FAERS reports 20370267 and 20345235. Notably, some of these cases appear to have been serious in nature. Therefore, the review team recommends the addition of a Warning and Precaution to the MOV Fact Sheet for Health Care Providers and that the risk of hypersensitivity reactions be described in the MOV Fact Sheet for Patients.

Rash Adverse Events

A total of 10 FAERS reports regarding rash-type adverse events have been received to date. These rash events were generally not associated with systemic signs or symptoms, though one participant did report decreased temperature and another report mentioned a cough and decreased appetite (perhaps due to COVID-19) and mildly increased eosinophils. At least two patients were treated with Benadryl and one patient received systemic steroids. All available information from these reports is summarized in the table below.

Table 1. Summary of FAERS Reports for Rash Adverse Events

FAERS #	Age/Sex	Preferred Term(s)	Onset	Intervention	Outcome	Confounders	Comments
20334071 USA	43F	Erythema, flushing	Day 2	Discontinued MOV	Not reported		Happened again day after she had stopped MOV. No dyspnea or swelling.
20345133 USA	41M	Rash, rash erythematous, rash pruritic, skin reaction	Day 2	Discontinued MOV	Not reported	Quetiapine, Flexeril, amitriptyline, lisinopril, buspirone	
20347766 USA	33F	Systemic lupus erythematosus rash	Day 1	Discontinued MOV	Not reported	Spiroinolactone	Patient developed "bad sunburn" covering nose and cheeks. Only reported PMH is asthma and acne.
20347777 USA	51F	Body temperature decreased, feeling cold, rash, skin discoloration	After 2 nd dose.	Discontinued MOV	Resolved	Prior episodes of getting cold and fingertips turning white.	Rash on abdomen. Temperature decreased to 93°F. Resolved with warm tea and blankets.
20355859 USA	20F	Erythema, rash, urticaria	Day 5	Discontinued MOV (only 1 dose left)	Not reported		
20355972 USA	73M	Rash	Day 3	Discontinued MOV and started Benadryl	Not reported		
20363371 USA	62M	Rash	Day 4	Discontinued MOV	Not reported		
20376978 Japan	36F	Urticaria	Day 5	Completed MOV, took "anti-allergic drugs"	Resolved		The physician assessed urticaria as MOV-related as "there were no other factors other than MOV"

20378789 USA	32M	Hyperhidrosis, rash, urticaria	Day 1	Discontinued MOV, started Benadryl	Ongoing	HIV	Still experiencing hives 5 days after stopping MOV.
20407630 Japan	58M	Drug eruption, cough, decreased appetite	Day 2	Discontinued MOV, started prednisolone then changed to Decadron	Resolving		Eosinophils reported as “mildly increased”

Abbreviations: F, female; HIV, human immunodeficiency virus; M, male; MOV, molnupiravir; PMH, past medical history.

As described in the table, several of these events occurred in patients receiving other medications that may be associated with rashes (i.e., FAERS reports 20345133 and 20347766). Another case (FAERS report 20378789) was confounded by a diagnosis of HIV, which may be associated with rash and urticaria. Lastly, there are reports of rash and urticaria as manifestations of COVID-19, which is a confounding condition for all of these cases.⁴ However, in the majority of the cases, the timing of the rash onset relative to the initiation of MOV raises concern that the rashes are MOV-related. Therefore, the review team recommends that these post-authorization reports of rash, erythema, and urticaria be described in the MOV Fact Sheet.

Summary of Fact Sheet Revisions Related to Safety:

- The following Warning and Precaution was added to the Healthcare Provider Fact Sheet:

5.2 Hypersensitivity Including Anaphylaxis

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

- Section 6 of the Healthcare Provider Fact Sheet was updated to include the following:

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of molnupiravir . 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

- Section 17 of the Healthcare Provider Fact Sheet (Patient Counseling Information) was also updated to include the following:

Hypersensitivity Reactions

⁴ Abuelgasim, E, ACM Dona, RS Sondh, A Harky, 2021, Management of Urticaria in COVID-19 Patients: A Systemic Review, *Dermatol Ther*, 34(1):e14328.

Inform patients that hypersensitivity reactions have been reported, even following a single dose of molnupiravir, 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.

- The Patient Fact Sheet was updated to include these new hypersensitivity safety events.

Regulatory Conclusion and Associated Actions:

Based on the above, the Division of Antivirals and Office of Infectious Diseases recommends revision to EUA 108 consistent with the above is appropriate to protect the public health.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)

These highlights of the EUA do not include all the information needed to use molnupiravir under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for molnupiravir.

MOLNUPIRAVIR capsules, for oral use

Original EUA Authorized Date: 12/23/2021

Revised EUA Authorized Date: 02/2022

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR 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 molnupiravir	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 MOLNUPIRAVIR

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved molnupiravir, 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. Molnupiravir is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- Molnupiravir 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 molnupiravir 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.

Molnupiravir 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 molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir 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 molnupiravir 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 molnupiravir 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)
- Molnupiravir 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 molnupiravir authorized under this EUA. (4)

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity:** Molnupiravir is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions,** including anaphylaxis have been reported with molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir. (5.2)
- Bone and Cartilage Toxicity:** Molnupiravir 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 \geq 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to molnupiravir (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 molnupiravir authorized under this EUA. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy:** The use of molnupiravir 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 molnupiravir. (8.1, 8.3)
- Lactation:** Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. 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 molnupiravir. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR 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 molnupiravir, the following steps are required. Use of molnupiravir 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 molnupiravir. 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 molnupiravir 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. Molnupiravir 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 molnupiravir. [see *Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use*].
 - iii. There are benefits and risks of taking molnupiravir 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 molnupiravir.
 - 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, molnupiravir may cause fetal harm when administered to pregnant individuals. If molnupiravir is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of molnupiravir 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 molnupiravir during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of molnupiravir use during pregnancy, as outlined in the “Fact Sheet for Patients and Caregivers,” were discussed with the patient.

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 molnupiravir within 7 calendar days from the healthcare provider's awareness of the event [see *Adverse Reactions (6.4)*].

For information on clinical studies of molnupiravir 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 molnupiravir 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 website¹ 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

- Molnupiravir is not authorized for use in patients who are less than 18 years of age [see *Warnings and Precautions (5.3)*].
- Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19². Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 [see *Dosing and Administration (2.1)*].
- Molnupiravir is not authorized for use for longer than 5 consecutive days.
- Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Molnupiravir 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 molnupiravir belongs (i.e., anti-infectives).

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

Prior to initiating treatment with molnupiravir, 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 molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir 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.

Information Regarding Available Alternatives for the EUA Authorized Use

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 for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

Other therapeutics are currently authorized for the same use as molnupiravir. 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>.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of Molnupiravir in Adult Patients

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 molnupiravir 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)*].

Molnupiravir 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 molnupiravir 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 molnupiravir, 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 molnupiravir authorized under this EUA.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.

5.1 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended for use during pregnancy. When considering molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir 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 molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir 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 molnupiravir and for 4 days after the final dose [see *Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)*].

Prior to initiating treatment with molnupiravir, 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 molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity

Molnupiravir 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 molnupiravir 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 molnupiravir 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 molnupiravir may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to molnupiravir 800 mg twice daily in clinical trials. The safety assessment of molnupiravir 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 molnupiravir 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 molnupiravir (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 molnupiravir and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the molnupiravir 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 Molnupiravir in MOVE-OUT*

	Molnupiravir N=710	Placebo N=701
Diarrhea	2%	2%
Nausea	1%	1%
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 molnupiravir. 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 molnupiravir 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 "Molnupiravir 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

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 molnupiravir.

*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 molnupiravir authorized under this EUA. No clinical drug-drug interaction trials of molnupiravir 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 molnupiravir 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 molnupiravir 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, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir 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 molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir 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 molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and

potential benefits and potential risks of using molnupiravir 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 molnupiravir, breastfeeding is not recommended during treatment with molnupiravir 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 molnupiravir [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.

8.3 Females and Males of Reproductive Potential

Based on animal studies, molnupiravir may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing

Prior to initiating treatment with molnupiravir, 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 molnupiravir [see *Warnings and Precautions (5.1)*].

Males

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir 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 molnupiravir. The risk beyond three months after the last dose of molnupiravir 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

Molnupiravir 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 molnupiravir 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 molnupiravir. 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/1.73m² 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)*].

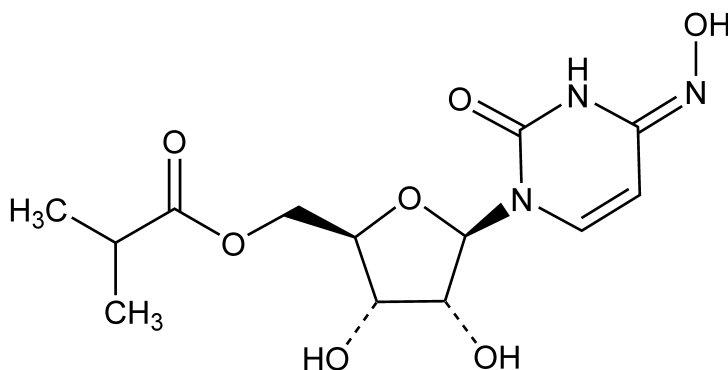
10 OVERDOSAGE

There is no human experience of overdosage with molnupiravir. Treatment of overdose with molnupiravir 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

Molnupiravir is 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 C₁₃H₁₉N₃O₇ 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 molnupiravir 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 molnupiravir.

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

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 Molnupiravir Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
AUC _{0-12hr} (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 _{0-12hr} (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 (<i>in vitro</i>)	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

Molnupiravir 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/1.73m² 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

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 (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) 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.

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 CC₅₀ 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 CC₅₀ 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

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 molnupiravir 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 molnupiravir 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-eight percent of subjects received molnupiravir 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

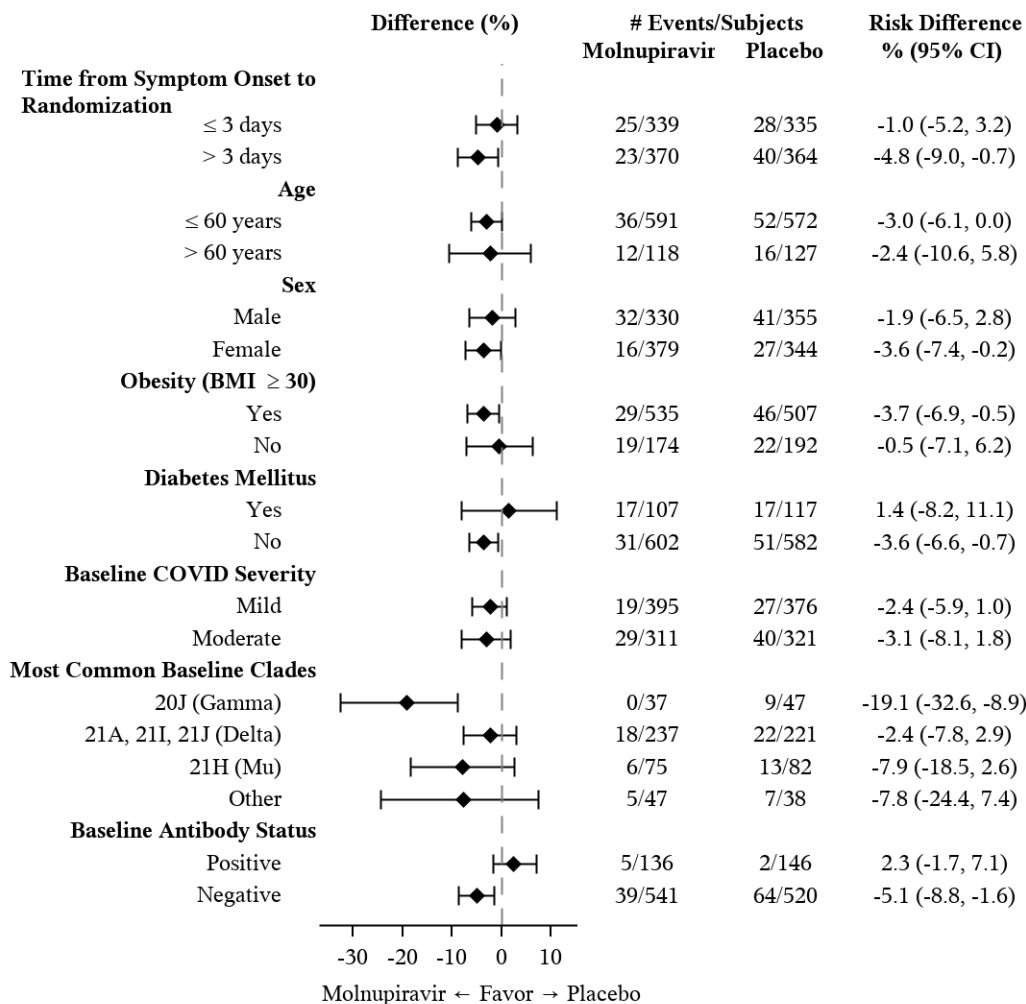
baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics 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 \geq 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*

Molnupiravir (N=709)	Placebo (N=699)	Adjusted Risk Difference % (95% CI)
n (%)	n (%)	
All-cause hospitalization \geq24 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%)	
<p>*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 molnupiravir 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.</p> <p>Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).</p> <p>Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (\leq3 days vs. $>$3 [4-5] days).</p>		

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



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

Molnupiravir 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 molnupiravir 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

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 molnupiravir [see *Box*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been reported, even following a single dose of molnupiravir, 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 molnupiravir 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 molnupiravir and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir 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 molnupiravir and for at least 3 months after the last dose of molnupiravir. The risk beyond 3 months after the last dose of molnupiravir 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

Molnupiravir 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 molnupiravir during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy surveillance program. Advise patients who have taken molnupiravir 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 molnupiravir and for 4 days after the last dose of molnupiravir. 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 molnupiravir [see *Use in Specific Populations (8.2)*].

Administration Instructions

Inform patients to take molnupiravir with or without food. Advise patients to swallow molnupiravir capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of molnupiravir 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)*].

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

 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

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**Fact Sheet for Patients And Caregivers
Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019
(COVID-19)**

What is the most important information I should know about molnupiravir?

Molnupiravir may cause serious side effects, including:

- **Molnupiravir may cause harm to your unborn baby. It is not known if molnupiravir will harm your baby if you take molnupiravir during pregnancy.**
 - Molnupiravir is not recommended for use in pregnancy.
 - Molnupiravir has not been studied in pregnancy. Molnupiravir was studied in pregnant animals only. When molnupiravir was given to pregnant animals, molnupiravir caused harm to their unborn babies.
 - You and your healthcare provider may decide that you should take molnupiravir 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 molnupiravir during pregnancy, you and your healthcare provider should discuss the known and potential benefits and the potential risks of taking molnupiravir 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 molnupiravir and for 4 days after the last dose of molnupiravir. Talk to your healthcare provider about reliable birth control methods.
- Before starting treatment with molnupiravir your healthcare provider may do a pregnancy test to see if you are pregnant before starting treatment with molnupiravir.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with molnupiravir.

Pregnancy Surveillance Program:

- There is a pregnancy surveillance program for individuals who take molnupiravir 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 molnupiravir 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 molnupiravir during pregnancy to Merck Sharp & Dohme Corp. by calling 1-877-888-4231 or [pregnancyreporting.msd.com](https://www.msd.com/pregnancyreporting).

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

- It is not known if molnupiravir can affect sperm. While the risk is regarded as low, animal studies to fully assess the potential for molnupiravir to affect the babies of males treated with molnupiravir have not been completed. A reliable method of birth control (contraception) should be used consistently and correctly during treatment with molnupiravir 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

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

You are being given this fact sheet because your healthcare provider believes it is necessary to provide you with molnupiravir 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 molnupiravir 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). Molnupiravir is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about molnupiravir. Talk to your healthcare provider about your options if you have any questions. It is your choice to take molnupiravir.

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 molnupiravir?

Molnupiravir 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 molnupiravir 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.

Molnupiravir 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 molnupiravir?

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 molnupiravir?

- Take molnupiravir exactly as your healthcare provider tells you to take it.
- Take 4 capsules of molnupiravir every 12 hours (for example, at 8 am and at 8 pm)
- **Take molnupiravir for 5 days.** It is important that you complete the full 5 days of treatment with molnupiravir. Do not stop taking molnupiravir before you complete the full 5 days of treatment, even if you feel better.
- Take molnupiravir 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 molnupiravir 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 molnupiravir to make up for a missed dose.

What are the important possible side effects of molnupiravir?

- See, “**What is the most important information I should know about molnupiravir?**”
- **Allergic Reactions.** Allergic reactions can happen in people taking molnupiravir, even after only 1 dose. Stop taking molnupiravir 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 molnupiravir are:

- diarrhea
- nausea
- dizziness

These are not all the possible side effects of molnupiravir. Not many people have taken molnupiravir. 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?

Like molnupiravir, FDA may 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 molnupiravir. 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 molnupiravir and for 4 days after the last dose of molnupiravir. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about your options and specific situation before taking molnupiravir.

How do I report side effects with molnupiravir?

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 molnupiravir?

- Store molnupiravir capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep molnupiravir 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 molnupiravir 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.

Molnupiravir 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.

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 molnupiravir is in effect for the duration of the COVID-19 declaration justifying emergency use of molnupiravir, unless terminated or revoked (after which molnupiravir may no longer be used under the EUA).

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 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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