

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

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

-----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 progressing 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. 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 (5.2)
 - 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)
- 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. (5.2, 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 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. There are no adequate, approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at high risk for progressing to severe COVID-19, including hospitalization or death.
 - iii. 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>.
 - iv. There are benefits and risks of taking molnupiravir as outlined in the “Fact Sheet for Patients and Caregivers.”
 - v. Merck Sharp & Dohme has established a pregnancy surveillance program.
 - vi. 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.
 - vii. 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, 5.2)*, *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 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* (5.2)].
- 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.

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.

Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits [see *Warnings and Precautions (5.1, 5.2)*, *Use in Specific Populations (8.1, 8.3)* and *Nonclinical Toxicology (13.1)*].

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

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 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.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is 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 recommends 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: d poc.usa@msd.com

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with molnupiravir.

Serious adverse events are defined as:

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

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, 5.2)*].

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 (5.2) 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)*].

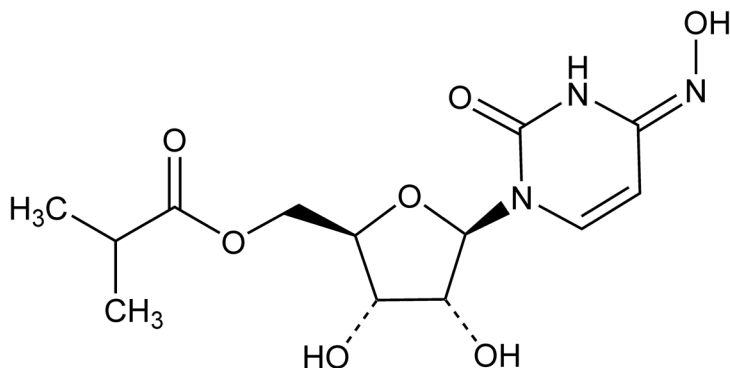
10 OVERDOSAGE

There is no human experience of overdose 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 (5.2) 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.

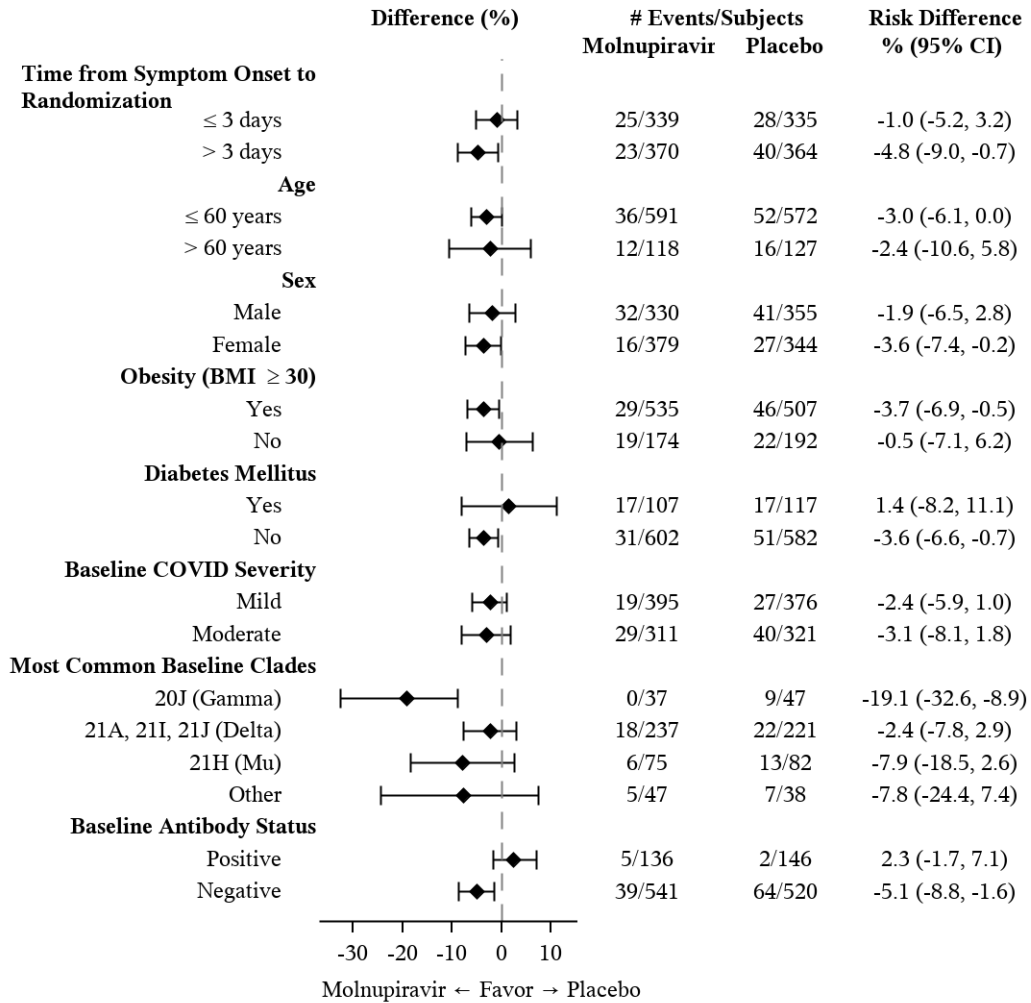
Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥ 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 ≥ 24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	
*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received 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.		

Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).
 Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤ 3 days vs. >3 [4-5] days).

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



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

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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*].

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 (5.2) 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

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

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