FACT SHEET FOR HEALTHCARE PROVIDERS: INTERIM AUTHORIZATION OF MOLNUPIRAVIR

HIGHLIGHTS OF INTERIM AUTHORIZATION

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

MOLNUPIRAVIR capsules, for oral use

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER INTERIM AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------INTERIM AUTHORIZATION OF MOLNUPIRAVIR----------

The Health Sciences Authority (HSA) has granted an Interim Authorization to permit the emergency use of the therapeutic product, molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis for the treatment of mild to moderate COVID-19 in patients aged 18 years and above who are at high risk for progressing to severe COVID-19 and/or hospitalization, and in whom alternative COVID-19 treatment options are not clinically appropriate.

The efficacy and safety of molnupiravir in the vaccinated population has not been established. In the clinical study, the subgroup analysis in patients who were sero-positive at baseline indicating recent or current infection response has shown a higher proportion of patients in the molnupiravir arm progressing to hospitalization or death compared to placebo (14).

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.

Treatment with molnupiravir should only be initiated after the clinicians have carefully assessed that the potential benefits outweigh the risks (5.1, 5.3, 8.1, 8.3, 13.1).

----------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 Interim Authorization. (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 ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

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

No drug interactions have been identified based on the limited available data. (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 INTERIM AUTHORIZATION

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

1. Treatment of mild-to-moderate COVID-19 patients aged 18 years and above who are at high risk for progressing to severe COVID-19 and/or hospitalization, and in whom alternative COVID-19 treatment options are not clinically appropriate.

2. Treatment with molnupiravir should only be initiated after the clinicians have carefully assessed that the potential benefits outweigh the risk *[see Warning and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

3. 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.

4. The prescribing healthcare providers must inform the patient/caregiver that:
    i. There are benefits and risks of taking molnupiravir as outlined in the "Fact Sheet for Patients and Caregivers."
    ii. 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.
    iii. 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.
5. 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)]*.

6. The prescribing healthcare provider and/or the provider's designee is/are responsible for reporting of all medication errors and serious adverse events potentially related to molnupiravir *[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 AUTHORIZED USE

Molnupiravir is authorized for use under an Interim Authorization for the treatment of mild to moderate COVID-19 in patients aged 18 years and above who are at high risk[1] for progressing to severe COVID-19 and/or hospitalization, and in whom alternative COVID-19 treatment options are not clinically appropriate.

The efficacy and safety of molnupiravir in the vaccinated population has not been established. In the clinical study, the subgroup analysis in patients who were sero-positive at baseline indicating recent or current infection response has shown a higher proportion of patients in the molnupiravir arm progressing to hospitalization or death compared to placebo. *[see Clinical Studies (14)]*.

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-19[2]. 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.

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[1] The risk factors included in the clinical study were age >60 years, active cancer, chronic kidney disease (excluding dialysis or eGFR <30 mL/min/1.73 m^2), chronic obstructive pulmonary disease, obesity (BMI ≥30 kg/m^2), serious heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), diabetes mellitus.

[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.

Treatment with molnupiravir should only be initiated after the clinicians have carefully assessed that the potential benefits outweigh the risks *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

Authority for Issuance of the Interim Authorization

The interim authorization for the abovementioned emergency therapeutic product by the Health Sciences Authority (HSA) of Singapore is made under Regulations 60A(4) and (5)(b) of the Health Product (Therapeutic Products) Regulations.

HSA issued this interim authorization, based on MSD's request and submitted data.

For authorized uses, although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that molnupiravir may be effective for the treatment of mild to moderate COVID-19 in patients aged 18 years and above who are at high risk for progressing to severe COVID-19 and/or hospitalization, and in whom alternative COVID-19 treatment options are not clinically appropriate as specified in this Fact Sheet.

For additional information about Interim Authorization, visit HSA at: https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/psar-emergency-therapeutic-product.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage 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 Authorized Use (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 Interim Authorization.

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.

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 Interim Authorization. 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

6.3 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for reporting of all serious adverse events* and medication errors potentially related to 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.

7 DRUG INTERACTIONS

No drug interactions have been identified based on the limited available data. 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

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*). 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/1.73 m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

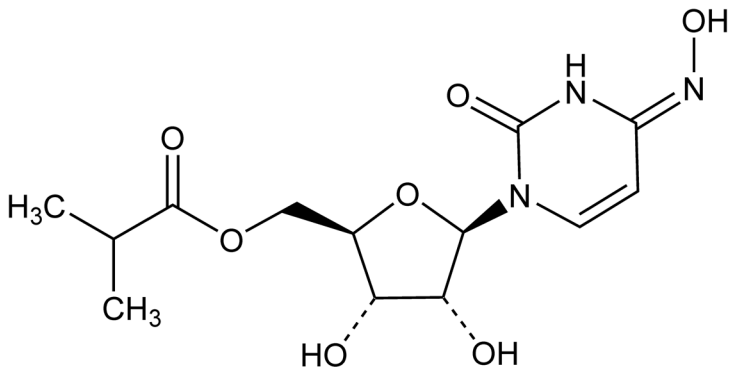
10 OVERDOSAGE

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 $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



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

Each 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	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]

Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)
Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated. *Values were obtained from population PK analysis. †Median [min - max]	

Specific Populations

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

Pediatric Patients

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/1.73 m^2 or on dialysis.

Patients with Hepatic Impairment

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

Drug Interaction Studies

In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of

OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP 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 (USA-WA1/2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.66 μM in A-549 cells and 0.32 to 2.03 μM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.1.1, BA.2, BA.4 and BA.5) with mean EC_{50} values of 0.55-2.95 μM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Viral RNA Rebound

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 after initiating study treatment in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 after initiating study treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

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 CC_{50} values ranging from 7.5 μM (human lymphoid CEM cell line) to >100 μM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 μM and 7.7 μM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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 Interim Authorization 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. In the subgroup analysis in patients who were sero-positive at baseline indicating recent or current infection response, a higher proportion of patients in the molnupiravir arm progressed to hospitalization or death compared to placebo.

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

Molnupiravir (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)

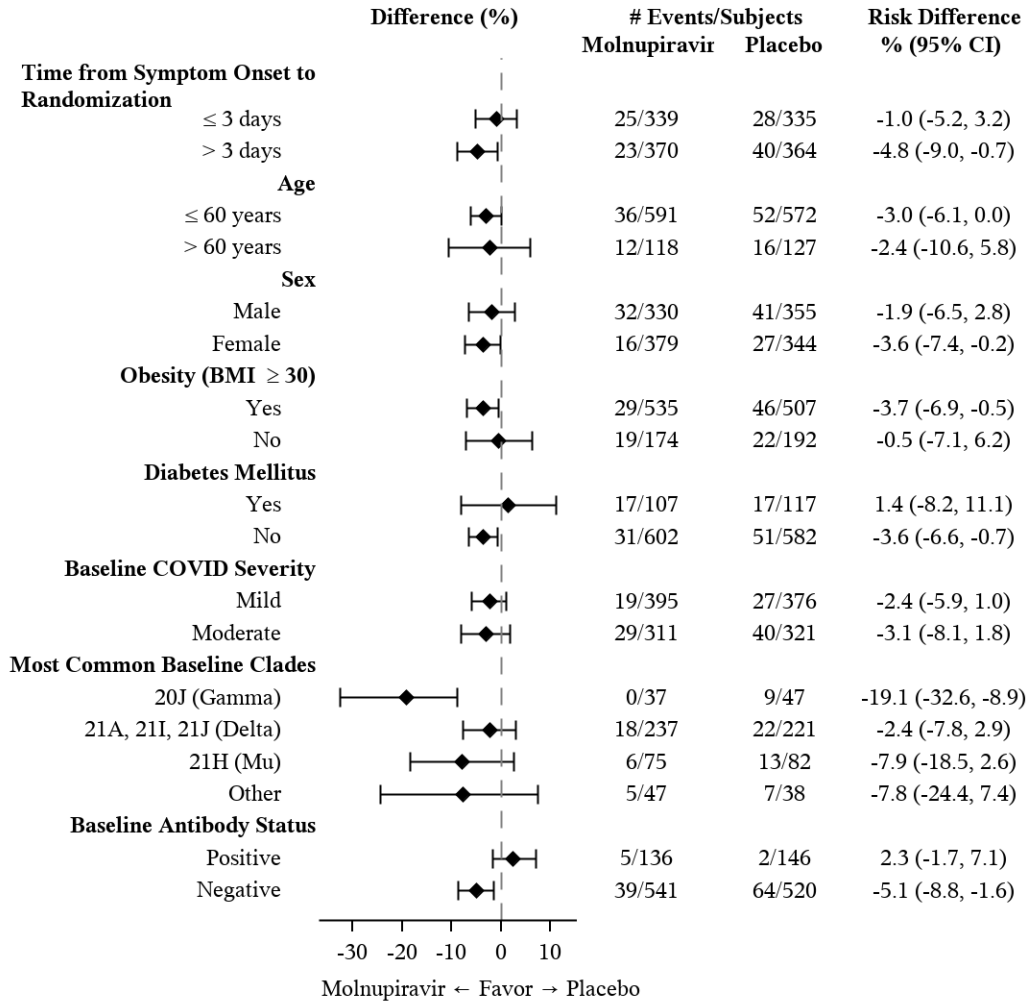
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received 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
200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and	40 count bottles

	“82” printed in white ink	

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”.

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)]*.

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

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

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